Official Title: A Phase I Safety and Pharmacokinetics Study to Evaluate a Human Monoclonal Antibody (MAB) VRC-HIVMAB095-00-AB (10E8VLS) Administered Alone or Concurrently with MAB VRC- HIVMAB075-00-AB (VRC07-523LS) Via Subcutaneous Injection in Healthy Adults

ClinicalTrials.gov Identifier: NCT03565315

Document Type:

- Redacted Study Protocol (Statistical Analysis Considerations located in Section 6 of the Protocol 2.0)
- Redacted IRB-approved Informed Consents – Main and Supplemental (final versions)

Document/Date:

- Protocol Version 2.0: July 9, 2018
- IRB-approved Main Informed Consent Version 2.0: Posted September 12, 2018
- IRB-approved Supplemental Informed Consent Version 2.0: Posted September 12, 2018

Version 2.0
09 July 2018

VACCINE RESEARCH CENTER
Protocol VRC 610
(18-I-0113)

A PHASE I SAFETY AND PHARMACOKINETICS STUDY TO EVALUATE A HUMAN MONOCLONAL ANTIBODY (MAB) VRC-HIVMAB095-00-AB (10E8VLS) ADMINISTERED ALONE OR CONCURRENTLY WITH MAB VRC- HIVMAB075-00-AB (VRC07-523LS) VIA SUBCUTANEOUS INJECTION IN HEALTHY ADULTS

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

Clinical Trial Sponsored by:
NIAID, VRC
Bethesda, Maryland

IND Sponsored by:
NIAID, VRC Bethesda, Maryland

IND 137085 - held by VRC

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IRB Initial Review Date: 21 May 2018

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

Abbreviation	Term
10E8VLS	an antibody with specificity to the membrane proximal external region and proximal viral membrane lipid of gp41
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
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
β-HCG	human chorionic gonadotropin
bNAb	broadly-neutralizing human monoclonal antibody
CBC	complete blood count
CL	clearance
Cmax	maximum concentration
CRS	cytokine release syndrome
cGMP	current Good Manufacturing Practice
DNA	deoxyribonucleic acid
EAE	expedited adverse event
EC50	Half-maximal effective concentration
EDTA	Ethylenediaminetetraacetate
ELISA	enzyme-linked immunosorbent assay
Env	envelope
EOI	end of infusion; end of injection
F	bioavailability
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLT	(green) lithium heparin tube
gp	glycoprotein
HBcAb	Hepatitis B core antibody
HCV Ab	Hepatitis C virus antibody
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRPP	Human Research Protections Program
IB	Investigator's Brochure
IgG1	Immunoglobulin G1
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
L	liter

Abbreviation	Term
LIMS	Laboratory Information Management System
λz	terminal slope of concentration vs time profile
MAb	monoclonal antibody
mcg	microgram
mg	milligram
mL	milliliter
mM, mmol	millimole
MSD	Meso Scale Discovery
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH CC	National Institutes of Health Clinical Center
NHP	Non-human primate
OHRP	Office for Human Research Protections
PBMC	peripheral blood mononuclear cells
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PI	Principal Investigator
PK	pharmacokinetic
PSRT	Protocol Safety Review Team
Q	Inter-compartmental clearance
QA	quality assurance
RSC	Regulatory Support Center
SAE	serious adverse event
SC	subcutaneous
SHIV	simian-human immunodeficiency virus
SST	serum separator tube
TCR	tissue cross reactivity
T½	half-life
Tmax	time of maximal concentration (Cmax)
UNAIDS	Joint United Nations Programme on HIV/AIDS
UP	unanticipated problem
USP	United States Pharmacopeia
Vd	volume of distribution
VITL	Vaccine Immunology Testing Lab
VRC	Vaccine Research Center
VRC07-523LS	an antibody with specificity to the CD4 binding site of gp120
WBC	white blood cell

PRÉCIS

VRC 610: A Phase I Safety and Pharmacokinetics Study to Evaluate a Human Monoclonal Antibody (MAB) VRC-HIVMAB095-00-AB (10E8VLS) Administered Alone or Concurrently with MAB VRC- HIVMAB075-00-AB (VRC07-523LS) Via Subcutaneous Injection in Healthy Adults

Study Design: This first-in-human, open-label study will evaluate MAb 10E8VLS (VRC-HIVMAB095-00-AB) administered alone or concurrently (i.e., at the same visit) with MAb VRC07-523LS (VRC-HIVMAB075-00-AB) in healthy adults ages 18 to 60. The primary hypothesis is that administrations of 10E8VLS alone and concurrently with VRC07-523LS will be well-tolerated in healthy adults. A secondary hypothesis is that both broadly neutralizing monoclonal antibodies (bNAbs) will be detectable in human sera with a definable half-life.

Product Description: The 10E8VLS and VRC07-523LS bNAbs target the HIV-1 envelope at distinct epitopes: 10E8VLS recognizes the membrane proximal external region (MPER) and proximal viral membrane lipid of gp41, while VRC07-523LS recognizes the CD4 binding site of gp120. Both antibodies are human in origin, contain two amino acid modifications within the C-terminus of the heavy chain constant region designed to improve antibody half-life *in vivo*, and were developed by the VRC/NIAID/NIH. The 10E8VLS and VRC07-523LS bNAbs are manufactured under cGMP regulations at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc., Frederick. MD.

The 10E8VLS drug product is supplied at a concentration of 100 ±10 mg/mL in a sterile, aqueous, buffered solution of 5.25 mL in single-use 10 mL glass vials. The VRC07-523LS drug product is supplied at a concentration of 100 ±10 mg/mL in an isotonic, sterile solution of 6.25 ± 0.1 mL in single-use 10 mL glass vials. Each drug product will be prepared in separate syringes.

Subjects: Healthy adults, 18-60 years of age.

Study Plan: This open-label study will include 4 dosing regimens of either 10E8VLS (5 mg/kg) alone or 10E8VLS (5 mg/kg) and VRC07-523LS (5 mg/kg). All injections will be administered by the subcutaneous (SC) route. For Groups 1 and 2, 10E8VLS will be administered once or three-times at 12-week intervals. For Groups 3 and 4, 10E8VLS and VRC07-523LS will be administered once or three-times at 12-week intervals, respectively. Enrollment will begin with Groups 1 and 2, followed by Groups 3 and 4.

VRC 610 Study Schema

Groups	Study Product(s)	Subjects per Group	Dose (mg/kg) Administered SC	Day 0	Week 12	Week 24
1	10E8VLS	3	5	X		
2	10E8VLS	3	5	X	X	X
3[1,2]	10E8VLS+ VRC07-523LS	5	5 of each MAb	X		
4[1,2]	10E8VLS+ VRC07-523LS	5	5 of each MAb	X	X	X
	Total Subjects[3]	16				

[1] Enrollment into Group 3 and 4 will commence after positive PSRT review of safety data from Groups 1 and 2 as described in Section 4.4.

[2] 10E8VLS and VRC07-23LS will be provided in separate syringes and administered at the same visit. See Section 4.2.3 for additional SC administration instructions for Groups 3 and 4 by anatomical site.

[3] The expected enrollment is 16 subjects with permitted increase to a total of 30 in case there are subjects who do not complete the schedule, additional pharmacokinetic (PK) evaluations are needed, enrollment of additional subjects is required for safety evaluations, or additional safety and PK data are needed to support potential expansion to multiple sites.

Study Duration: Study participation will be approximately 24 weeks for subjects in Groups 1 and 3, and 48 weeks for subjects in Groups 2 and 4.

1. INTRODUCTION

The human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) has remained a major global public health problem since the discovery of the virus in 1983. A 2017 report by the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 76.1 million people have been infected with HIV since the start of the epidemic, contributing to 35 million deaths from AIDS-related illnesses [1]. Despite these statistics, global incidences of new HIV infections have actually declined from peak rates in the mid-1990s; a reduction attributed in part to increased availability of antiretroviral therapy (ART) and the effective execution of prevention/treatment programs such as those that target mother-to-child transmission. Unfortunately HIV infection is extremely complex and none of the current therapeutic or prophylactic regimens can completely prevent or cure an infection or induce a full recovery of the host immune system. Thus, novel prevention and cure strategies are being investigated.

Advances in B-cell immunology utilizing single-cell cloning methods, next-generation sequencing, high throughput computational analysis techniques, and increased cell culture survivability procedures, have resulted in the isolation of an extensive group of broadly-neutralizing human monoclonal antibodies (bNAbs) to the HIV-1 envelope (env) structure. These include antibodies with specificity to the gp41 membrane proximal external region (MPER, 10E8 [2, 3]), the CD4 binding site (VRC07-523LS [4], VRC01 [5], N6 [6], 3BNC117 [7]); the high-mannose patch (10-1074 [8], PGT121 [9]); and the V2 apex (PG9 [10, 11], PGDM1400 [9], CAP256.25 [12]). The VRC/NIAID is investigating clinical applications of these bNAbs [2, 4, 6, 13]. This first-in-human Phase I study will investigate the safety and pharmacokinetics (PK) of 10E8VLS (a modified version of 10E8) as a single product or in combination with VRC07-523LS. A combination drug product serves to increase the breadth and potency of viruses neutralized by targeting different sites of vulnerability on the HIV Env protein and thus; potentially address the emergence of resistance.

The 10E8 wild-type monoclonal antibody (MAb) was isolated at the NIH from an HIV-1 slow progressor [2]. The MAb exhibited multiple promising characteristics for therapeutic and prophylactic applications, as evidenced by its ability to neutralize 98% of viruses in a 181-multiclade HIV-1 pseudovirus panel at an inhibitory concentration $(IC)_{50}$ of <50 µg/mL. Consonant with other HIV-1 specific bNAbs, the variable regions of both the heavy and light chain were highly somatically-mutated (21% and 14% respectively) compared to the germline sequence [2]. Epitope mapping studies determined that 10E8 not only bound within the gp41 MPER domain of the envelope protein, but had a marked binding preference for cholesterol-rich lipids, which is a distinct feature of the HIV-1 virion membrane. In contrast, its affinity for more typical cellular membrane lipid compositions [14-15] was shown to be much weaker, a key attribute underscored by the little to no autoreactivity observed in anionic phospholipid and HEp-2 cell binding studies. Subsequent modifications to the WT MAb to improve molecular solubility, stability, and potency [19]; and to incorporate the previously-described LS mutation in the constant or crystallizable fragment (Fc) region to increase neonatal Fc-receptor (FcRn) binding and consequent MAb half-life, produced 10E8VLS.

The VRC07 (wild-type) heavy chain was identified by 454 deep sequencing based on its similarity to the VRC01 MAb (originally discovered in an HIV-1-infected individual with a 15+ year history of viral control in the absence of anti-retroviral therapy [20]) and paired with the VRC01 (wild-type) light chain. Subsequent modifications of VRC07 consisting of structure-

guided optimization to improve neutralization potency with limited autoreactivity, and incorporation of the LS mutation in the Fc constant region to improve MAb half-life, and other mutations to enhance manufacturability, have yielded VRC07-523LS [21]. With these improvements, VRC07-523LS was able to neutralize 96% of viruses in a 179-multiclade HIV-1 pseudovirus panel at an IC_{50} of <50 µg/mL compared to 89% for VRC01, cementing its further development as a therapeutic and/or prophylactic agent against HIV.

1.1. Nonclinical Experience

The 10E8VLS and VRC07-523LS antibodies have each been evaluated in neutralization assays to assess for breadth and potency against a comprehensive panel of viral envelope pseudoviruses and/or viral isolates; proof-of-concept immunotherapy studies of SHIV-infected rhesus macaques; lipid and tissue cross-reactivity studies to assess for binding to antigenic determinants; and repeat-dose good laboratory practice (GLP) toxicity and pharmacokinetic studies to assess for safety overall. Experimental endpoints evaluated in the toxicity study included: moribundity/ mortality; physical examinations, clinical signs of toxicity, and injection site reactogenicity; body weights; food consumption; body temperatures; clinical pathology parameters (clinical chemistry, hematology, and coagulation); 10E8VLS or VRC07-523LS serum concentration levels; organ weights; gross pathology at necropsy; and microscopic pathology.

The nonclinical experience for 10E8VLS and VRC07-523LS is briefly summarized in Sections 1.1.1 and 1.1.2, respectively. More detailed information is provided in the respective Investigator's Brochure (IB) of each drug product (DP).

1.1.1. 10E8VLS

10E8VLS has demonstrated robust neutralization potency in in vitro neutralization studies, most notably by maintaining or even exceeding levels elicited by the parental MAb while retaining comparable breadth. Toxicity studies to investigate lipid binding showed low autoreactivity with 10E8VLS in an HEp-2 cell binding assay and anti-cardiolipin ELISA, and no prolongation of activated partial thromboplastin time (aPTT). Other toxicity studies conducted include a good laboratory practice (GLP) tissue cross-reactivity study to assess for binding to antigenic determinants in a full panel of normal human, cynomolgus monkeys, and Sprague-Dawley rat tissues; and a three-administration repeat-dose GLP toxicity and pharmacokinetic study in male and female Sprague-Dawley rats covering 10E8VLS dose levels of 40 and 400 mg/kg/dose by intravenous administration and 5 and 50 mg/kg/dose by SC administration. Detailed results of these studies are provided in the 10E8VLS IB.

1.1.2. VRC07-523LS

The increased neutralization potency (relative to VRC01/VRC01LS) *in vitro* and prolonged half-life of VRC07-523LS correlate with improved protection against SHIV infection *in vivo* in animal studies [21], suggesting a potential clinical application against HIV-1 infection in humans in preventive and/or therapeutic settings. In an 179-viral panel representing the major circulating HIV-1 genetic subtypes in individuals in the acute and chronic stages of HIV-1 infection, VRC07-523LS was able to neutralize 96% and 92% of primary HIV-1 isolates at an IC_{50} <50 µg/mL and IC_{50} <1 µg/mL, respectively; and 95% and 85% of HIV-1 isolates at an IC_{80} <50 µg/mL and IC_{80} <1 µg/mL, respectively. Passive immunization of rhesus macaques with VRC07-

523LS (20 mg/kg) prior to mucosal challenged with SHIV 5 days later conferred 100% protection to MAb-infused animals, while all control-treated animals became infected. Protection rates in animals infused with lower concentrations (0.05 or 0.2 mg/kg) of VRC07-523LS were 0 and 75%, respectively, and supported calculations to determine a correlate of protection based of the plasma MAb concentration that provides 50% protection.

Additional toxicity studies revealed VRC07-523LS displayed minimal to low reactivity to phospholipids, showed no impact on activated partial thromboplastin time (aPTT), and demonstrated limited to no reactivity to a panel of nuclear antigens. VRC07-523LS binding to HEp-2 cells was considered minimal. Although some positive staining to cytoplasmic sites was noted in the GLP TCR study, no membrane specific binding was observed to indicate there was any cross-reactivity of toxicologic concern. The GLP toxicity study showed 3-repeat administrations at 10-day intervals of VRC07-523LS at doses up to 400 mg/kg/dose IV or up to 40 mg/kg/dose SC, were well-tolerated as most findings were reversible and resolved by the recovery period. The IV or SC treatment regimen also produced acceptable VRC07-523LS concentration levels post-dose; however, only the high MAb IV administration resulted in sustained levels through Study Day 56. The no-observed-adverse-event levels (NOAELs) for this study were 400 mg/kg IV and 40 mg/kg SC.

Detailed results of these studies are provided in the VRC07-523LS IB.

1.2. Clinical Experience

There is no prior human experience with 10E8VLS alone or when administered concurrently with VRC07-523LS. However, several published reports of Phase I and II clinical data in HIV-1 infected persons have shown combination regimens of other HIV-1 bNAbs (i.e., 4E10, 2F5 and 2G12) to be generally safe and well-tolerated [22-25].

The only clinical experience for VRC07-523LS is derived from an ongoing Phase 1 clinical trial (VRC 605) in healthy adults, 18-50 years of age. As of 15 January 2018, 25 subjects have received at least one dose of VRC07-523LS, totaling 12 SC administrations (5 mg/kg dose level), and 25 IV infusions (dose level range from 1 to 40 mg/kg). Overall, all VRC07-523LS dose levels have been well-tolerated with no unexpected reactions. There have been no serious adverse events (SAEs) reported or study safety pauses for adverse events (AEs). Roughly 60% (15/25) of VRC07-523LS recipients have experienced at least one AE. Although the majority of these AEs have been mild to moderate in severity, one grade 3 and one grade 4 event was reported. The grade 3 AE was elevated creatinine that occurred 56 days after the last product administration and was most likely related to dehydration following exercise. The creatinine value represented an increase of 1.5 to 2 times the baseline value, which was still well within the institutional normal range, but was determined to be a grade 3 based on the DAIDS Grading Table. The grade 4 AE was elevated liver enzymes, likely related to starting a concomitant medication known to cause hepatoxicity (i.e., fluoxetine) and deemed to be not related to VRC07-523LS. Subsequent product administrations were discontinued for this subject due to the concomitant illness. While the subject was being followed for safety, liver enzyme tests fluctuated again after starting citalopram which reinforced the initial attribution 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 and did not result in hospitalization, jaundice, coagulopathy,

bleeding, or ascites. Six (6) mild or moderate AEs were assessed as related to study product; all have resolved without residual effects.

Two subjects developed infusion reactions shortly after IV product administration. The pattern and temporal onset of these symptoms were typical of reactions observed with other monoclonal antibodies [26]. Briefly, one 40 mg/kg IV recipient 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 and all symptoms resolved within 12 hours. The second subject was in the 20mg/kg IV group and experienced 3 separate infusion reactions (n=2 moderate, n=1 mild that occurred following the product administration 3) after each product administration. 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.

Solicited local reactions reported in the week after any VRC07-523LS administration have included mild bruising at the IV administration site in 1/17 (5.9%) subjects, and mild pain/tenderness at the SC injection site in 5/8 (62.5%) subjects. For solicited systemic reactogenicity symptoms reported in the 3 days after any VRC07-523LS administration, 4/17 (25%) subjects who received the product intravenously have experienced one or more symptoms. These have included malaise (2 mild, 1 moderate), myalgia (2 mild, 1 moderate), headache (2 mild), and chills (2 moderate). Five (5) of 8 (62.5%) subjects who received the product subcutaneously have experienced one or more solicited systemic reactogenicity symptoms. Reported symptoms were all been mild and included malaise (3 events), myalgia (2 events), headache (3 events), chills (1 event), nausea (1 event), and joint pain (2 events).

Interim PK results based on preliminary data have estimated the average compartmental half-life of VRC07-523LS at 33 ±10 days, with an estimated 28 day trough after one 5 mg/kg SC administration calculated at 27 (12) µg/mL. Data necessary to calculate the VRC07-523LS clearance rate or half-life at each dose and route are not yet available.

1.3. Rationale for the Study Design

Animal and *in vitro* models of HIV infection have suggested bNAbs reactive to antigenically diversified Env proteins expressed by quasispecies of circulating virus may hold significant promise as immunoprophylactic and/or therapeutic agents to thwart the subversive effects of HIV on the immune system. Both 10E8VLS and VRC07-523LS can mediate extraordinary breadth and potency against various HIV isolates. Their potency in pseudovirus neutralization assays may indicate less MAb is needed overall to mediate an effect, offering the possibility of subcutaneous administration as a more feasible approach to immunoprophylaxis. Moreover, a combination MAb strategy involving bNAbs that target independent epitopes on the HIV-1 envelop may exert additive effects on neutralization activity and reduce the likelihood of viral resistance and escape [27, 28].

This study is the first-in-human trial to evaluate the safety of a single- or three, repeat-dose regimen of 10E8VLS administered alone, and concurrently with VRC07-523LS, via SC injection. The 5 mg/kg SC MAb dose and regimens to be used in this trial were selected based on prior clinical experience with other HIV-1 bNAbs (VRC01, VRC01LS, and VRC07-523LS [29, 30, 31, and unpublished observations]) that used these same parameters. Subjects assigned to

receive both 10E8VLS and VRC07-523LS will be dosed at the combined antibody dose level of 10 mg/kg, which is lower than the dose levels for 10E8VLS (40 to 400 mg/kg IV and 5 and 50 mg/kg SC) or VRC07-523LS (40 to 400 mg/kg IV and 40 mg/kg SC) examined in two separate rat GLP toxicity studies performed with each antibody. A 12-week interval for repeat-dosing has been used in clinical trials with VRC01LS [31] and VRC07-523LS [unpublished data] and will allow for a direct comparison of 10E8VLS and VRC07-523LS (as applicable) serum MAb concentrations at identical time-points to facilitate pharmacokinetic (PK) profile comparisons.

Future clinical use of bNAb therapy for prophylactic or therapeutic indications would likely require multiple dose administrations. Thus, testing a combination bNAb regimen in a setting of multiple administrations will provide a better definition of safety and provide insight into the effects on PK when more than one MAb is administered concurrently.

1.4. Research-specific Laboratory Assessments

The research assays described in this section are designed to characterize the investigational product rather than assess the health of the subjects. Laboratory assessments in this Phase 1 study will include PK analysis, evaluation for anti-drug antibody (ADA) development following product exposure, and ex vivo analysis to assess the neutralization activity of 10E8VLS alone and cumulatively in co-recipients of 10E8VLS and VRC07-523LS.

1.4.1. Pharmacokinetic (PK) Analysis

Concentrations of 10E8VLS and VRC07-523LS for the PK analyses will each be measured separately by qualified ELISAs using a Beckman Biomek based automation platform, as previously described [29]. Briefly, the 10E8VLS or VRC07-23LS anti-idiotypic MAb is coated onto Immulon-4HXB microtiter plates overnight at 4° C. Plates are washed and blocked (10% FBS in PBS) for 2 hours at room temperature. Duplicate serial 3-fold dilutions covering the specific range (100 – 218,700) of the test sample are incubated for 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. Linear regression of a standard curve of 10E8VLS or VRC07-523LS covering the range from 5-200 ng/mL or 5 to 125 ng/mL, respectively, is utilized to quantitate the sample concentrations of each antibody based upon the average of sample dilutions within the range of the assay.

1.4.2. Anti-drug Antibody (ADA) Analysis

A three-level algorithm will be used to screen, confirm, and functionally characterize for ADA in the clinical serum samples according to FDA guidance [32]. Screening and confirmation will involve a Meso Scale Discovery (MSD) electrochemiluminescence (ECL) bridging assay. Briefly, biotinylated 10E8VLS or VRC07-523LS is immobilized onto a streptavidin-coated MSD plate (capture molecule). Serial dilutions of subject sera and a fixed amount of SULFO-TAG 10E8VLS or VRC07-523LS (reporter molecule) are then added to the plate. Any ADA present in the serum will bind both the biotinylated and SULFO-TAG-labelled 10E8VLS or VRC07-523LS and form a complex. The ADA assay will be conducted on batched samples collected at baseline, 4-weeks post each product administration, and at the last study visit. It may also be assessed at other time-points if there is a clinical indication or the PK analysis shows a substantial decrease in 10E8VLS or VRC07-523LS concentration. Method development to

confirm ADA activity in clinical serum samples that also contain 10E8VLS alone or with VRC07-523LS are ongoing and not presently available. However, the stored clinical serum samples will be tested once the assay is qualified.

1.4.3. HIV Pseudovirus Neutralization

Subject sera collected (but not limited to) at baseline (Day 0), and at 72 hours, 12 weeks, and 16 weeks post each product administration may be evaluated to assess the functional capacity of passively administered 10E8VLS and/or VRC07-523LS to neutralize pseudotyped HIV viruses using an *in vitro* cell-based virus neutralization assay as previously described for VRC01 [6, 29, 30, 33].

1.4.4. Allotype-specific Effects

Exploratory evaluation to detect for theoretical IgG1 allotype-specific effects may be performed in cases when PK measures suggest a reduced 10E8VLS or VRC07-523LS MAb half-life or an ADA response [34-36]. Coded stored samples will be used for evaluation of the genetic sequence of the immunoglobulin heavy chain constant region allotype.

2. INVESTIGATIONAL PRODUCTS

2.1. 10E8VLS and VRC07-523LS Overview

The 10E8VLS and VRC07-523LS are bNAbs that target distinct epitopes on the HIV-1 envelope. 10E8VLS recognizes the membrane proximal external region (MPER) and proximal viral membrane lipid of gp41, while VRC07-523LS recognizes the CD4 binding site of gp120. Both antibodies are human in origin, contain two amino acid modifications within the C-terminus of the heavy chain constant region designed to improve MAb half-life in vivo, and were developed by the VRC/NIAID/NIH. The 10E8VLS and VRC07-523LS antibodies are manufactured under cGMP regulations at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc., Frederick. MD.

2.2. Manufacturing and Drug Product Production

Each drug substance (DS) is manufactured separately under cGMP using a stable transfected CHO-DG44 cell line. Purification steps include an initial harvest by membrane-based clarification and diafiltration into chromatography buffer, followed by protein-A affinity chromatography, low pH treatment of the eluate, and anion exchange membrane chromatography. The eluate is then subjected to a 20 nm virus reduction filtration step, followed by concentration and diafiltration into the final formulation buffer, prior to filtering with a 0.22 μm-filter. The DS concentration of each MAb is determined and filled into containers for storage at ≤ -65°C until further formulation is required.

The 10E8VLS drug product is supplied at a concentration of 100 ±10 mg/mL in a sterile, aqueous, buffered solution of 5.25 mL in single-use 10 mL glass vials. The VRC07-523LS drug product is supplied at a concentration of 100 ±10 mg/mL in an isotonic, sterile solution of 6.25 ± 0.1 mL in single-use 10 mL glass vials. Each DP should be stored at -35°C to -15°C.

More details on the composition and manufacturing of 10E8VLS and VRC07-523LS is provided in each respective IB.

3. STUDY OBJECTIVES

3.1. Primary Objectives

- To evaluate the safety and tolerability of a 5 mg/kg SC dose of 10E8VLS administered once, or three-times by repeat-dosing every 12 weeks, in healthy adults.
- To evaluate the safety and tolerability of a 5 mg/kg/MAb SC dose of 10E8VLS and of VRC07-523LS administered once, or three-times by repeat dosing every 12 weeks, in healthy adults.

3.2. Secondary Objectives

- To evaluate the pharmacokinetics of 10E8VLS through 24 weeks after the last dose in recipients administered 10E8VLS once or three-times.
- To evaluate the pharmacokinetics of 10E8VLS and VRC07-523LS through 24 weeks post-dosing in recipients administered 10E8VLS and VRC07-523LS once or three-times.

3.3. Exploratory Objectives

- To determine whether an anti-drug antibody (ADA) response to 10E8VLS can be detected in 10E8VLS recipients.
- To determine whether an ADA response to either 10E8VLS or VRC07-523LS can be detected in recipients of both antibodies.
- To assess the neutralization potential of 10E8VLS in sera samples obtained at representative time-points throughout the study from 10E8VLS only recipients.
- To assess the neutralization potential of 10E8VLS and VRC07-523LS in sera samples obtained at representative time-points throughout the study from recipients of both 10E8VLS and VRC07-523LS.
- To assess for IgG1 allotypes by PCR and allotype-specific effects on 10E8VLS PKs in recipients of 10E8VLS alone and 10E8VLS and VRC07-523LS.
- To assess for the IgG1 allotypes by PCR and allotype-specific effects on VRC07-523LS PKs in recipients of 10E8VLS and VRC07-523LS.

4. STUDY DESIGN AND CLINICAL PROCEDURES

This open-label study will include 4 dosing regimens, as shown in Table 1. Subjects will be administered a 5 mg/kg dose of 10E8VLS either once (Group 1) or three-times at 12-week intervals (Group 2). Subjects in Group 3 and 4 will be concurrently administered 5 mg/kg doses of 10E8VLS and of VRC07-523LS either once or three-times at 12-week intervals, respectively. All injections will be administered via the subcutaneous (SC) route.

Table 1: VRC 610 Study Schema

Groups	Study Product(s)	Subjects per Group	Dose (mg/kg) Administered SC	Day 0	Week 12	Week 24
1	10E8VLS	3	5	X		
2	10E8VLS	3	5	X	X	X
3[1,2]	10E8VLS+ VRC07-523LS	5	5 of each MAb	X		
4[1,2]	10E8VLS+ VRC07-523LS	5	5 of each MAb	X	X	X
Total Subjects[3]		16				

[1] Enrollment into Groups 3 and 4 will commence after positive PSRT review of safety data from Groups 1 and 2. See Section 4.4 for further details.

[2] 10E8VLS and VRC07-23LS will be provided in separate syringes and administered at the same visit. See Section 4.2.3 for additional SC administration instructions for Groups 3 and 4 by anatomical sites.

[3] The expected enrollment is 16 subjects with permitted increase to a total of 30, in case there are subjects who do not complete the schedule, additional pharmacokinetic (PK) evaluations are needed, enrollment of additional subjects is required for safety evaluations, or additional safety and PK data are needed to support potential expansion to multiple sites.

The study will begin with the enrollment of Groups 1 and 2. Because there is no prior human experience with 10E8VLS, the first product administration of 10E8VLS alone (Groups 1 or 2), and of 10E8VLS and VRC07-523LS (Groups 3 or 4), will trigger a wait of at least 3 days before any subsequent subjects are administered the study product(s). Throughout the 3-day evaluation period, safety data (as described in Section 4.3) will be reviewed by a Protocol Safety Review Team (PSRT) to determine if enrollments may continue. Activation and enrollment of Groups 3 and 4 will also be dependent upon review of safety data from Groups 1 and 2 by the PSRT as described in Section 4.4. The PSRT safety review decisions and the status of the enrollment process will be transparent and discussed during the weekly and/or monthly safety review. The composition of the PSRT is discussed in Section 8.8.

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

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

4.1. Study Population

All inclusion and exclusion criteria must be met for eligibility.

4.1.1. Inclusion Criteria

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

1) Willing and able to complete the informed consent process.
2) 18 to 60 years of age.
3) Based on history and examination, in good general health and without history of any of the conditions listed in the exclusion criteria.
4) Willing to have blood samples collected, stored indefinitely, and used for research purposes.
5) Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process.
6) Screening laboratory criteria within 84 days prior to enrollment must meet the following criteria:
   - White blood cell count (WBC): 2,500-12,000/mm^3.
   - WBC differential: Within institutional normal range or accompanied by the Principal Investigator (PI) or designee approval.
   - Platelets: 125,000 – 400,000/mm^3.
   - Hemoglobin: Within institutional normal range or accompanied by PI or designee approval.
   - Creatinine: ≤ 1.1 x Upper Limit of Normal (ULN).
   - AST: ≤ 1.25 x ULN
   - ALT: ≤ 1.25 x ULN.
   - Negative for HIV infection by an FDA approved method of detection.
   - Negative for Hepatitis B core antibody (HBcAb) and Hepatitis C virus antibody (HCV Ab).

Female-Specific Criteria:

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

4.1.2. Exclusion Criteria

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

1. Woman who is breast-feeding, or planning to become pregnant during the study.
2. Prior receipt of licensed or investigational monoclonal antibody.
3. Weight > 115 kg.
4. Any history of a severe allergic reaction with generalized urticaria, angioedema or anaphylaxis within the 2 years prior to enrollment that has a reasonable risk of recurrence during the study.

5. Hypertension that is not well controlled.
6. Receipt of any investigational study agent within 28 days prior to enrollment.
7. Any other chronic or clinically significant condition that in the opinion of investigator would jeopardize the safety or rights of the volunteer including (but not limited to): diabetes mellitus type I/II, chronic hepatitis; OR clinically significant forms of drug or alcohol abuse, asthma, autoimmune disease, psychiatric disorders, heart disease, or cancer.

4.2. Clinical Procedures and Laboratory Assays

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

4.2.1. Screening

Screening for this study will be completed through the VRC's screening protocol, VRC 500 (NIH 11-I-0164). Volunteers will be recruited through Institutional Review Board (IRB)-approved advertising. The evaluations and sample collection that will be included in screening are a medical history, physical exam, any clinical laboratory tests (as detailed in the SOE, Appendix II) needed to confirm eligibility, and pregnancy test for females of reproductive potential. Additional assessments of health may be conducted at screening based on clinical judgment. Research samples consisting of peripheral blood mononuclear cells (PBMCs) and serum will be collected. Informed consent documents will be reviewed. Counseling related to potential risks of the study product, pregnancy prevention and HIV risk-reduction will be performed. An Assessment of Understanding (AoU) will be completed in association with enrollment into VRC 610. Screening records will be kept to document the reason why an individual was screened but not enrolled. Only subjects determined to be eligible after screening is completed will be enrolled.

4.2.2. Enrollment, Study Days and Visit Numbers

In this study, enrollment is defined as the assignment of a study identification number and study group schedule in the clinical database. A clinician will discuss the target dates and timing of the study product administration(s) and sample collections before completing an enrollment to ensure the subject can comply with the projected schedule.

Day 0 is defined as the day of first product administration. Day 0 may occur on the same day as enrollment, or up to 6 weeks after enrollment. This period may be increased with PI approval. If Day 0 does not coincide with enrollment, then the enrollment day may be referred to by a negative number of days (i.e., Day -1 to Day -42). For calculating elapsed days following Day 0, each subsequent calendar date is labeled by the next sequential "Study Day" as shown in the SOE (Appendix II). Since there may be more than one research sampling timepoint of interest per study day, each sample collection timepoint has its own "Visit Number." For this reason, there may be more than one visit number recorded on the same calendar date.

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

4.2.3. Study Product(s) Administration

All study product administrations will be completed according to the assigned group. For women of childbearing potential, a negative pregnancy test must be obtained on the day of each product administration and prior to injection. Additionally, temperature, blood pressure, heart rate (pulse) and weight will be recorded and a targeted physical examination conducted, prior to each product administration. All subjects will be observed for at least 4 hours following any product administration. In addition, all subjects will receive an evening telephone safety check on the day of product administration.

The product will be administered by direct SC injection using needle and syringe. The clinician will use proper SC technique to ensure administration into SC fatty layer and a slow push to minimize discomfort or the excessive distention of overlying skin. Given the weight criterion in this study, the maximum volume needed to administer a 5 mg/kg SC dose per MAb is not expected to exceed 5.75 mL. Note that up to 4 SC injection sites per MAb may be used if deemed necessary by the clinician. Because Groups 3 and 4 will receive both 10E8VLS and VRC07-523LS, subjects in these groups may receive up to 8 total SC injections.

The SC administration site(s) to be used must be assessed as acceptable by the clinician and the subject. The preferred SC administration sites is the abdomen, but the posterior upper arms and anterior thighs may be used. One anatomic site will be used for single product administrations. For product administrations of 10E8VLS and VRC07-523LS (Groups 3 and 4), the same anatomic site(s) should be divided sagittally and each MAb injected into opposite sides as summarized in Table 2. All SC injections should be at least 2 inches apart. The anatomic location(s) used for administration of each drug product will be noted in the source documents.

Table 2: SC Administration Instructions For Groups 3 and 4 by Anatomical Site
Appendix I

Selected Anatomical Site	Instructions for SC Administration
Abdomen	Divide the abdomen sagittally and give 10E8VLS SC injections into the left side and VRC07-523LS injections into the right side or vice versa.
Arms	Give 10E8VLS SC injections into the posterior upper left arm and VRC07-523LS injections into the posterior upper right arm or vice versa.
Thighs	Give all 10E8VLS SC injections into the anterior left thigh and all VRC07-523LS injections into the anterior right thigh or vice versa.

4.2.4. Solicited Adverse Events and Clinical Follow-up

Subjects will be given a 3-day diary (paper or electronic-based), a thermometer, and a ruler. The subjects will use the diary daily as a memory aid to record their highest temperature, local and systemic symptoms experienced, and concomitant medications taken for 3 days after product administration. Subjects will be provided training on diary completion, proper thermometer usage, and use of the ruler to measure injection site bruising, swelling and redness. Completion of diary card training will be noted in the source documents. Note that while the electronic diary is preferred, subjects will have the option to use a paper diary instead. The paper diary if used, will be transcribed into the study database and stored in the subject file for monitoring purposes.

The signs and symptoms solicited by diary will include systemic events of unusually tired/feeling unwell, muscles aches (outside the injection site), headache, chills, nausea and joint pain; and local events of pain/tenderness, swelling, redness, bruising, and pruritus. Subjects will record their highest measured temperature daily for assessment of fever and largest measured diameter of redness, swelling, and bruising at all injection sites of each mAb. Subject diaries will be reviewed by a clinician for accuracy and completeness at follow-up visits. No attribution assessment will be performed for solicited events reported in the diary. Clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved within 3 days.

Diary data will be available in real-time for subjects who use the electronic diary; the clinician may contact the subject by phone if any moderate or severe side effect is reported. Events that may require a clinic visit include rash, urticaria, fever of 38.6˚C (Grade 2) or higher lasting greater than 24 hours or significant impairment in the activities of daily living (ADL) (such as those consistent with Grade 2 or higher impairment). Additionally, arthralgia or other clinical concerns may prompt a study visit based on the judgment of a study clinician.

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

4.2.5. Pharmacokinetics

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

4.2.6. Schedule of Evaluations (SOE)

The SOE (Appendix II) provides details on the study schedule and the permitted visit windows. Schedule 1 is for the group assigned to receive one SC dose of 10E8VLS alone (Group 1), or of 10E8VLS and VRC07-523LS (Group 3). Schedule 2 is for the group assigned to receive three-repeat doses of 10E8VLS alone (Group 2) or of 10E8VLS and VRC07-523LS (Group 4). After enrollment, deviations from the visit windows are discouraged but will be permitted at the discretion of the PI or designee; and will be recorded as protocol deviations. If any subject in Groups 2 and 4 discontinue product administration, a modified study schedule will be followed (Schedule 3).

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

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

4.2.7. Concomitant Medications

Routine prescription, over-the-counter (OTC) medications, and herbal supplements will be entered in the database at the time of enrollment. Subsequently, concomitant medications

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

4.3. Criteria for Dose Continuation

The first product administration of 10E8VLS alone (Groups 1 or 2), and of 10E8VLS and VRC07-523LS (Groups 3 and 4), will trigger a wait of at least 3 days before any subsequent subjects are administered the assigned study product(s). During this period, the 24-hour post product administration safety labs and clinical evaluation, the 48- and 72-hour clinical assessments, and the 3-day diary card entries will be reviewed by the PSRT. If deemed safe, dosing may continue and the remainder of subjects in the respective groups will be enrolled. The decision to continue dosing will be documented in the study files.

4.4. Criteria for Dose Group Activation and Repeat-Dosing

The activation of each dose group and authorization for repeat-dosing will proceed in a staged manner that is governed by the outcome of planned PSRT Data Reviews summarized in Table 3.

Table 3: Schema for Repeat-Dosing and Activation of Two MAb Dose Groups

PSRT Data Review Objective	Minimum Evaluable Safety Data	Favorable Review Outcome
Data Review #1		
• 10E8VLS repeat-dosing at 5 mg/kg SC	All post-administration safety data from Day 0 through the Day 14 visit in at least 6 subjects in Groups 1 and 2.	• Proceed with second and third doses in Group 2.
• Activation of the 2-MAb Dose Groups		• Proceed with enrollment of Groups 3 and 4.
Data Review #2		
• 10E8VLS and VRC07-523LS repeat-dosing at 5 mg/kg/MAb SC	All post-administration safety data from Day 0 through the Day 14 visit in at least 6 subjects in Groups 3 and 4.	• Proceed with second and third doses in Group 4.

If the first product administration is not completed or there are discontinuations from the study before there are sufficient data to conduct each PSRT Data Review, then extra subjects may be enrolled in order to have data on the requisite number of subjects. Additionally, the PSRT may requests enrollment of additional subjects into the relevant group(s) for further evaluation of AEs assessed as related to the study product(s) to support activation of, or authorize repeat-dosing in, a specific group.

The IRB will be provided with documentation of the safety review process and notification of all PSRT decisions made during a formal Data Review. Consultation with the IRB and notification of the FDA, if needed, as per study pause criteria (Section 4.7) will occur if indicated by the review.

4.5. Criteria for Subject Discontinuation from Protocol Participation

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

- Subject voluntarily withdraws;
- The IND Sponsor or regulatory authorities stop the study; or
- The PI assesses that it is not in the best interest of the subject to continue participation in the study or that the subject's compliance with the study is not sufficient.

4.6. Criteria for Discontinuation of Study Product (108EVLS and/or VRC07-523LS) Administration

Under certain circumstances, a subject may be discontinued from receiving further study product administrations. These include (but are not limited to):

- Pregnancy (female subjects only);
- Grade 3 AE assessed as related to the study product(s) (with the exception of self-limited Grade 3 solicited reactogenicity);
- Grade 4 AE assessed as related to the study product(s);
- Immediate hypersensitivity reaction associated with the study product(s);
- Intercurrent illness that is not expected to resolve prior to the next scheduled study product(s) administration AND for which PI (or designee) believes is in the best interest of the subject to restrict further exposure;
- Repeated failure to comply with protocol requirements;
- Co-enrollment into a study to receive another investigational research product prior to completion of the requisite study follow-up following the last study product(s) administration;
- The IND sponsor or the study PI decide to terminate the study;
- The IRB, Office for Human Research Protections (OHRP) or the FDA halt the study.

Subjects who have received at least one dose of the study product(s) but have been discontinued from further study product(s) administrations, will continue with follow-up as shown in Schedule 3 of the SOE with the following exceptions: research sample collections may be discontinued for pregnant women or others in which it is contraindicated.

4.7. Criteria for Pausing and Resuming the Study

Administration of the study product and new enrollments will be paused by the PI if any of the following criteria is met:

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

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

Plan for Review of Pauses and Resuming Rules:

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

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

5. SAFETY AND ADVERSE EVENTS

5.1. Adverse Events

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

Severity of AEs will be assessed using the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Even*ts, Corrected Version 2.1 [July 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf. Additional information can be found in Appendix III.

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

5.2. Serious Adverse Events

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

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

5.3. Adverse Event Reporting to the IND Sponsor

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

- results in death
- is life threatening
- results in persistent or significant disability/incapacity

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

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

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

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

5.4. IND Sponsor Reporting to the FDA

The IND Sponsor is responsible for making the determination of which SAEs are "serious and unexpected suspected adverse reactions" (SUSARs) as defined in 21 CFR 312.32.

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

All SUSARs (as determined by the IND Sponsor) will be reported to the FDA as IND Safety Reports; IND Safety Reports will also be provided to the IRB.

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

5.5. Reporting to the Institutional Review Board

5.5.1. Unanticipated Problem (UP) Definition

"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, Investigator's Brochure, other study documents or in consideration of the characteristics of the subject population being studied; **and**
- Related to participation in the research; **and**
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Unanticipated Problem: A UP that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

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

5.5.2. 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.

A Serious Protocol Deviation is defined as any deviation that meets the definition of an SAE or compromises the safety, integrity of the data, welfare or rights of subjects or others.

5.5.3. Non-Compliance Definition

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

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

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

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

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

5.5.4. Expedited Reporting to the NIAID IRB

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

- 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.

5.5.5. Annual Reporting to the NIAID IRB

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

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

6. STATISTICAL CONSIDERATIONS

6.1. Overview

This is a phase I study in healthy adults to assess the safety and pharmacokinetics of 10E8VLS administered alone and with VRC07-523LS by SC injection. Recruitment will target about 16 healthy adults, 18 to 60 years of age, as shown in Table 1. The permitted accrual is 30 subjects to allow for additional enrollments in the event that there are subjects who do not complete the schedule, or if additional PK or safety evaluations are needed.

6.1.1. Treatment Assignments

The Advantage eClinical system (EMMES Corp, Rockville, MD) will be used to assign subjects to a dose group in active accrual at the time of enrollment. If an enrolled subject is discontinued from the study before he/she has received any study product, a new eligible subject may be enrolled into the same group. If a replacement is needed in the case of a subject withdrawal, the replacement subject will be assigned to the same treatment as the dropout subject in order to complete the safety dataset as planned.

6.1.2. Sample Size Considerations

Although the study is primarily descriptive, the primary goal is to identify safety concerns associated with different dosages in group sizes ranging from 3 to 5 subjects. For a group size of 3 subjects, there is a 90% chance of observing at least 1 SAE if the true event rate is ≥ 0.536 and a 90% chance of observing no SAE if the true event rate is ≤ 0.034. For a group size of 5 subjects, there is a 90% chance of observing at least 1 SAE if the true rate is ≥ 0.37 and a 90% chance of observing no SAE if the true rate is ≤ 0.02. The probabilities of observing 0 and 1 or more events are presented in Table 4 for a range of possible true event rates. These calculations provide a complete picture of the sensitivity of this study design to identify potential safety problems with the study agent(s). For example, within the group of size n=3, if the true event rate is 0.01, then there is a probability of 0.97 to observe no event and a probability of 0.03 to observe at least 1 event; while, within the group of size n=5, if the true event rate is 0.1, then there is a probability of 0.59 to observe no events and a probability of 0.41 to observe 1 or more events.

Table 4: Event Probabilities for Different Scenarios

	Group Size, N=3		Group Size, N=5	
True Event Rate	Probability, No Events Observed	Probability, ≥ 1 Event Observed	Probability, No Events Observed	Probability, ≥ 1 Event Observed
0.01	0.97	0.03	0.95	0.05
0.03	0.91	0.09	0.86	0.14
0.05	0.86	0.14	0.77	0.23
0.1	0.73	0.27	0.59	0.41
0.2	0.51	0.49	0.33	0.67
0.3	0.34	0.66	0.17	0.83
0.4	0.22	0.78	0.08	0.92

Table 5 displays the upper and lower 95% exact binomial confidence bounds for all possible number of observed events in a group. For a group size of 3 subjects, the upper 95% exact

confidence bound on the true rate is 0.708 if no events are observed; the lower bound will be 0.292 if all subjects experience the event. Likewise, for a group size of 5 subjects, the upper 95% exact confidence bound of the true rate is 0.522 if no events are observed; symmetrically, the rate of the lower bound is 0.478 if all subjects experience the event.

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

Group Size, N=3		Group Size, N=5	
Observed Rate	**95% CI**	**Observed Rate**	**95% CI**
0/3	0, 0.708	0/5	0, 0.522
1/3	0.008, 0.906	1/5	0.005, 0.716
2/3	0.094, 0.992	2/5	0.053, 0.853
3/3	0.292, 1	3/5	0.147, 0.947
		4/5	0.284, 0.995
		5/5	0.478, 1.0

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

6.2. Statistical Analysis

6.2.1. Analysis Variables

The analysis variables will consist of baseline, PK, and safety variables to support analyses of the primary and secondary objectives.

6.2.2. Baseline Characteristics

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

6.2.3. Safety Analysis

The number and percentage of subjects with one or more AE and associated exact 95% confidence intervals will be summarized by dose group. Summaries will also include the number and percentage of subjects with any solicited or unsolicited AE, overall and by dose for each event.

Solicited Adverse Events:

Solicited AE data will be collected after each product administration of 10E8VLS and VRC07-523LS, as applicable. The number and percentage of subjects experiencing each type of solicited sign or symptom will be tabulated by severity, by dose group, and product. Subjects with multiple occurrences of the same event will be counted once using the event of highest severity.

Adverse Experiences:

All unsolicited AEs reported through 56-days post each product administration will be recorded and coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The number and percentages of subjects with each unsolicited AE will be tabulated by severity and relationship to the study product, and by dose group and pooled 10E8VLS only or 10E8VLS/VRC07-523LS dose groups. Subjects with multiple

occurrences of the same event will be counted once using the event of highest severity or strongest relationship to the study treatment.

A by-subject listing of all unsolicited AEs will provide details including severity, relationship to the study product, seriousness, new medical condition status, onset and end date, 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.

6.2.4. Tolerability Evaluation

The tolerability of an investigational medicinal product represents the degree to which overt adverse effects can be tolerated by the subject [37]. VRC 610 will be the first trial of 10E8VLS administered with and without VRC07-523LS in healthy adults. The tolerability evaluation will be mostly descriptive summaries of the frequency of solicited AE reports with an onset in the 3 days following each study product administration and subject withdrawals or discontinuations based upon subject discomfort or AEs. This early assessment of tolerability to the study product(s) will inform the parameters to solicit or routinely assess in future studies to further characterize the tolerability profile in a larger subject cohort.

6.2.5. Pharmacokinetics Analysis

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

Individual Subject Pharmacokinetic Analysis: A non-compartmental PK analysis will be performed using Phoenix (Certara) or a similar program on the VRC07-523LS and 10E8VLS concentration data generated from each subject. Calculated PK parameters will include: area-under-the-curve (AUC), maximum concentration (C_{max}), time to C_{max} (T_{max}), apparent clearance (CL/F), terminal slope (λz) and $T_{1/2(\lambda z)}$. C_{max} and T_{max} will be taken directly from the observed concentration-time data. The terminal slope, λz, will be determined from the terminal log-linear portion of the curve following the final dose in subjects with data available for more than 84 days (84D) post final dose. $T_{1/2(\lambda z)}$ will be calculated as $0.693/\lambda z$. $AUC_{0\text{-}Clast}$ will be determined using the linear trapezoidal method. If the final sample (C_{last}) has measurable 10E8VLS or VRC07-523LS concentrations, the remaining AUC after the final concentration ($AUCC_{last\text{-}inf}$) will be estimated as $C_{last/\lambda z}$. The 10E8VLS $AUC_{0\text{-}84D}$ will also be determined by trapezoidal method and used to compare the initial $AUC_{0\text{-}84D}$ between single and multiple dose administration. Data will be summarized by study group.

Population Pharmacokinetic Analyses: Population PK analyses will be performed on the 10E8VLS and VRC07-523LS PK data following administration to determine compartmental PK parameters with the program NONMEM (version 7.2 or later). A two compartment PK model will be used for this analysis based on prior clinical and pre-clinical pharmacokinetic analyses of bNAbs, including 10E8VLS and VRC07-523LS. Due to the small number of subjects receiving VRC07-523LS in the current study, the VRC07-523LS population PK analysis may be leveraged by incorporating population PK parameter estimates from prior VRC07-523LS PK studies. The

population PK analyses will generate estimates for initial and final apparent volumes of distribution (Vd1/F and Vd2 /F), apparent inter-compartmental clearance (Q/F) and CL/F. Vdss/F will be calculated as the sum of Vd_1/F and Vd_2/F. The compartmental, half-life, $T_{1/2(\beta)}$, will be calculated from CL/F. Vd_1/F, Vd_2/F and Q/F using standard pharmacokinetic equations. The population PK analysis will not include exploratory covariate analysis to assess factors as fixed effects associated with 10E8VLS PK parameters except for single versus multiple dose and concomitant VRC07-523LS. Individual subject empiric Bayesian post-hoc values for CL/F, Vdss/F and $T_{1/2beta}$ will also be determined. Final population PK model selection will be based on changes in the objective function and graphically by goodness of fit plots. The final population models will be assessed using bootstrap analyses. The study's 10E8VLS dosing strategy of 5 mg/kg SC every 12 weeks and its ability to achieve and maintain target 10E8VLS concentrations greater than 10 μg/mL will be performed using the final population PK model and Monte Carlo simulations with at least 5000 replicates.

6.2.6. Interim Analyses

Preliminary PK analyses may be done once per dose group as data is obtained. This may be performed before a dose group's PK data is complete and may only generate a subset of the final PK parameters. The interim analyses will be used to inform decisions about dose levels to assess in future studies with 10E8VLS, with and without VRC07-523LS co-administration.

7. PHARMACY PROCEDURES

The dose groups and dosing schedule for 10E8VLS alone and with VRC07-523LS are shown in Table 1. Refer to the 10E8VLS and VRC07-523LS IBs for detailed information about each product.

7.1. Study Products

10E8VLS (VRC-HIVMAB095-00-AB) is filled at a concentration of 100 ±10 mg/mL in a sterile, aqueous, buffered solution of 5.25 mL in 10 mL glass vials. Vials contain a clear, light yellow liquid that is essentially free of visible particles, although some small white to translucent particles inherent to the product may be present. The formulation buffer is composed of 10 mM Acetate/Phosphate, 50 mM NaCl, 100 mM Arginine, 5 % Sucrose, and 0.05% Pluronic F68 (poloxamer 188) at pH 6.75.

VRC07-523LS (VRC-HIVMAB075-00-AB) is supplied at a concentration of 100 ±10 mg/mL in an isotonic, sterile solution of 6.25 ± 0.1 mL in a 10 mL glass vial. Vials contain a clear, colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose, and 2.5% sorbitol at pH 6.8.

Vials containing 10E8VLS and VRC07-523LS are intended for single-use only and thus do not contain a preservative.

7.1.1. Administration Regimen

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 5 and 6 mL can be withdrawn from a vials containing 10E8VLS and VRC07-523LS, respectively. In this trial, dose is limited or established based on subject weight. The table below presents an example of the amount of 10E8VLS or VRC07-523LS needed for a 115 kg subject (the upper weight limit per protocol) assigned to receive a 5 mg/kg dose of each MAb.

Table 6: Sample Schematic for Determining the Number of Study Product Needed to Dose a 115 kg subject

MAb	MAb Nominal Concentration	MAb Nominal Volume	Total mg of MAb Needed for a 115 kg Person at 5 mg/kg Dose level	Total Volume of MAb Needed for a 115 kg Person at 5 mg/kg Dose level	MAb Vials Needed
10E8VLS	100 mg/mL	5 mL	575 mg	5.75 mL	2 vials
VRC07-523LS	100 mg/mL	6 mL	575 mg	5.75 mL	1 vial

7.1.2. 10E8VLS and VRC07-523LS Vialed Products

As designated on the product label, vials containing 10E8VLS or VRC07-523LS should be stored at -35°C to -15°C for long-term storage. At the clinical site, 10E8VLS and VRC07-523LS vials should be stored in a qualified, continuously monitored, temperature-controlled freezer; temperature excursions from -45°C to -10°C are acceptable.

7.1.2.1. 10E8VLS

Following thaw, 10E8VLS vials may be stored for up to 12 hours at room temperature (maximum 27°C) and/or up to 2 weeks at 2ºC to 8ºC if unused and unopened. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, sealed vials must be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 60 minutes to reduce viscosity and ensure accurate dose measurement.

7.1.2.2. VRC07-523LS

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

7.2. Temperature Excursions

The site pharmacist must promptly report any storage temperature excursions outside of the normal allowance for the storage device to the IND Sponsor (Appendix I). 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 Product for Administration

This section describes how the site pharmacist will prepare the study product for administration and how the clinician will administer the product. Clinician instructions on how to select an administration site are discussed in Sections 4.2.3 and 7.3.1.

10E8VLS and VRC07-523LS are highly concentrated protein solutions. Vials containing 10E8VLS and VRC07-523LS may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2ºC to 8ºC.

The following instructions apply to thawing 10E8VLS and VRC07-523LS:

1. Thaw vial(s) for a minimum of 1.5 hour at controlled room temperature (maximum 27°C) after removing from the freezer.
2. Keep the material at room temperature during the entire preparation period until use, up to the maximum storage times described in Section 7.1.2.
3. Prior to preparation for administration, vials should be swirled for 30 seconds with sufficient force to resuspend any visible particles, yet avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, return the vials to 2°C to 8°C storage. If the particles dissolve within the maximum storage times described in Section 7.1.2, the vials may be used for product preparation. **If particles continue to be observed, do not use the vialed product for SC administration**. Refrigerated product must be equilibrated at controlled room temperature (maximum 27ºC) for a minimum of 30 minutes before preparation and must be used within 8 hours of any subsequent return to room temperature.

4. If the thawed material is not administered within 24 hours of thaw, follow the storage information provided in Section 7.1.2.

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 for 10E8VLS or VRC07-523LS can be found in the IB for each drug product.

7.3.1. Study Product(s) Preparation for SC Administration

For each SC administration order, the subject's weight, dose level, study group and subject ID code will be included in the pharmacy order. To prepare a SC administration dose, the pharmacist will calculate the total mg needed and retrieve the minimum number of thawed, particle free vials needed to prepare the full dose. Prior to preparation for administration, vials should be gently swirled for 30 seconds avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, follow instructions in Section 7.3.

The needed volume of 10E8VLS or VRC07-523LS must be withdrawn from the vial into 1 to 4 syringes (BD Luer-Lok 3 mL syringe; REF # 309657 or other sizes of BD Luer-Lok syringes) using a 5 micron filter needle (BD Blunt Fill Needle – Filter , 18G 1 ½ inch; REF# 305211). A new filter needle must be used for each syringe. The filter needle must be discarded prior to dispensing and replaced with a needle suitable for SC injection at the time of administration.

7.3.2. Study Product(s) Administration Instructions by Anatomical Site

The clinician will use proper SC technique to ensure administration into the SC fatty layer and a slow push to minimize discomfort or the excessive distention of overlying skin. The preferred SC administration site is the abdomen; however, the posterior arms and anterior thighs may also be used. One anatomic site will be used for a single product administration (Groups 1 and 2). For product administrations of 10E8VLS and VRC07-523LS (Groups 3 and 4), the same anatomic site(s) should be used and each MAb given in a distinct region on opposite sides as summarized in below: The anatomic location(s) used for administration of each drug product will be noted in the source documents.

Abdomen: Divide the abdomen into quadrants and give 10E8VLS SC injections into the left 2 quadrants and VRC07-523LS injections given into the right 2 quadrants or vice versa.

Arms: Give 10E8VLS SC injections into the posterior upper left arm and VRC07-523LS injections into the posterior upper right arm or vice versa.

Thighs: Give 10E8VLS SC injections into the anterior left thigh and VRC07-523LS injections into the anterior right thigh or vice versa.

7.3.3. Handling of Prepared Product(s) for SC Administration

After preparation in syringes for SC administration, the prepared 10E8VLS or VRC07-523LS may be stored at 2ºC to 8ºC for up to 24 hours, or at room temperature (maximum 30ºC) for up to 4 hours, and should be administered within 4 hours after the product removal from a freezer. The product may not be stored in direct sunlight.

7.4. Labeling of Study Product

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

7.5. Study Product Accountability

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

7.6. Study Product Disposition

Empty and partially used vials must be discarded on the same day of use in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy. Any unopened vials that remain at the end of the study will be returned to the production facility or discarded at the discretion of the sponsor in accordance with policies that apply to investigational agents. Partially used vials may not be administered to other subjects or used for *in vitro* experimental studies.

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 describes the investigational product to be used and all aspects involved in protocol participation.

Before a subject's participation in the study, it is the investigator's responsibility to obtain written informed consent from the subject, 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(s) is/are administered. The Assessment of Understanding quiz must be completed before the study consent is signed.

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

8.2. Risks and Benefits

8.2.1. Risks

Risks of Administration of MAbs: Administration of MAbs may cause immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies. However, these reactions are rare and more often associated with MAb targeted to human proteins or with the use of murine monoclonal antibodies which would have a risk of human anti-mouse antibodies [38]. In this regard, 10E8VLS and VRC07-523LS are expected to have a low risk of such side effects since both are directed against the HIV envelope and are human in origin.

Typically, the side effects of MAbs are mild but may include reactions at the injection site (pain, redness, bruising, swelling), fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain. Clinical use of MAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections [38]; however, this is not expected to be a risk for a MAb targeted to a viral antigen.

Published experience with other human MAbs directed against the cell surface targets on lymphocytes has shown that infusion of a MAb may be associated with cytokine release, causing a reaction known as "cytokine release syndrome" (CRS) [39]. Most infusion-related events occur within the first 24 hours after beginning administration. Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension and hypoxia, are infrequent and more often associated with MAbs targeted to human proteins or when a non-human MAb, such as a murine MAb, is used [38]. 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, administration of histamine blockers and restarting the infusion at a slower rate [40].

Delayed allergic reactions to other MAbs may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the MAb and is noted to be more common with chimeric types of MAbs [38].

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

Risks of Blood Drawing: Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken.

8.2.2. Benefits

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

8.3. Institutional Review Board

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

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

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

8.4. Subject Confidentiality

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

8.5. Plan for Use and Storage of Biological Samples

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

8.5.1. Use of Samples, Specimens and Data

Samples, specimens and data collected under this protocol may be used to conduct protocol-related safety and immunology evaluations, exploratory laboratory evaluations related to the biological target of the study product, exploratory laboratory evaluations related to vaccine or infectious disease research in general and for research assay validation.

Genetic testing may be performed in accordance with the genetic testing information that was included in the study informed consent form (ICF).

Additional optional genetic testing, including transcriptome sequencing may be done on collected specimens in an effort to assess the expression of genes involved in the immune response to vaccination.

Results of genetic testing may have psychological implications for patients such as revelations regarding future health risks, incurable conditions, and/or information contradictory to stated biological relationships. Genetics counseling and advice will be available from the NIH to help subjects at all study sites with the implications of findings, where appropriate.

Following genetic testing, the data will be shared in a controlled-access public database for other investigators to benefit from it (e.g. the Database of Genotypes and Phenotypes dbGAP). However no personal, identifiable information will be shared in this process as the results will only be shared with a code.

Other optional analysis, including proteome, lipidome, metabolome, and exosome may be done on collected specimens to evaluate some proteins, lipids, metabolites, and low molecular weight molecules involved in the immune response to vaccination.

8.5.2. Storage and Tracking of Blood Samples and Other Specimens

All research samples use coded labels that only the VRC Clinic can link to the subject. Samples are stored at the VITL, Gaithersburg, MD or VRC Laboratories in Building 40, which are both secure facilities with limited access. Data will be kept in password-protected computers. Only investigators or their designees will have access to the samples and data. Samples will be tracked in the Laboratory Information Management System (LIMS) database or using another software designed for this purpose (e.g., Freezerworks or GlobalTrace).

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

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

At the time of protocol termination, samples will remain in the VITL facility or VRC laboratories or, after IRB approval, transferred to another repository. Regulatory oversight of the stored samples and data may be transferred to a stored samples protocol as part of the IRB-approved termination plan. Data will be archived by the VRC in compliance with requirements

for retention of research records, or after IRB and study sponsor approval, it may be either destroyed or transferred to another repository.

8.5.4. Loss or Destruction of Samples, Specimens or Data

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. Subject Identification and Enrollment of Study Participants

All study activities will be carried out at the NIH CC. Study subjects will be recruited through on-site and off-site advertising done for the screening protocol, VRC 500 (NCT 01375530). Effort will be made to include women and minorities in proportions similar to that of the community from which they are recruited and will be limited to persons at least 18 years of age and no older than 60 years of age at enrollment.

8.6.1. Participation of Children

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

8.6.2. Participation of NIH Employees

NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the "NIH 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 subjects who are NIH employees. The employee subject's privacy and confidentiality will be preserved in accordance with NIH Clinical Center and NIAID policies. For NIH employee subjects, consent will be obtained by an individual who is independent of the employee's team. If the individual obtaining consent is a co-worker to the subject, independent monitoring of the consent process will be included through the Bioethics Consultation Service. Protocol study staff will be trained on obtaining potentially sensitive and private information from co-workers or subordinates.

8.7. Compensation

Subjects will be compensated for time and inconvenience in accordance with the standards for compensation of the Clinical Research Volunteer Program. Study product administration visits will be $325. The compensation will be $175 for scheduled visits that include blood drawing,

$75 for clinic visits that do not include a blood draw or procedure, and $25 for the timely completion of each electronic diary.

8.8. Safety Monitoring

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

9. ADMINISTRATIVE AND LEGAL OBLIGATIONS

9.1. Protocol Amendments and Study Termination

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

The IND Sponsor, NIAID IRB, Office of Human Research Protections, study PI, and FDA reserve the right to terminate the study. The PI will notify the IRB in writing of the study's completion or early termination.

9.2. Study Documentation and Storage

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

Source documents are original documents, data, and records from which the subject's data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, microfiches, radiographs, and correspondence. Long-term storage of source documents may be in the form of electronic files.

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

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

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

All essential documentation should be retained by the institution for the same period of time required for medical records retention. The FDA requires study records to be retained for up to two years after marketing approval or refusal (21 CFR 312.62). No study document should be destroyed without prior written agreement between the VRC and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, they must notify the VRC in writing of the new responsible person and/or the new location.

9.3. Clinical Monitoring, Data Collection and Data Sharing

9.3.1. Clinical Monitoring Plan

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

requirements are met. Study monitoring visits will occur as defined by the IND Sponsor approved monitoring plan.

9.3.2. Data Collection

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

9.3.3. Source Documents

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

9.3.4. Data Sharing

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

9.4. Language

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

9.5. Policy Regarding Research-Related Injuries

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

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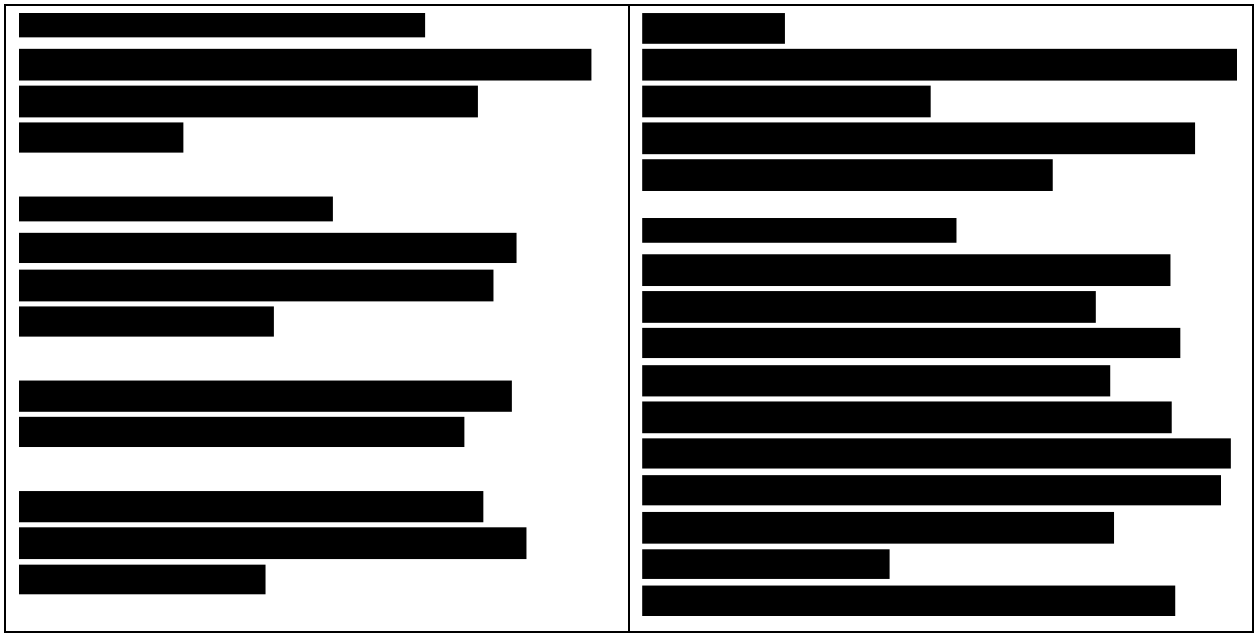
APPENDIX I: CONTACT INFORMATION

Contact Information

Contact Information



APPENDIX II: SCHEDULE OF EVALUATIONS

Schedule 1: SC Administration of 10E8VLS Alone (Group 1) or Concurrently with VRC07-523LS (Group 3)																	
Visit Number			01R	02	02A	03	04	05	06	07	08	09	10	11	15	16	17
Time After Injection				Pre	EOI	24hr	48hr	72hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study			-42 to -1	D0	D0	D1	D2	D3	D7	D14	D21	D28	D56	D84	D112	D140	D168
Clinical	**Tube**	**Screen**	**Enroll**	**Day of injection**													
VRC 500 Screening Consent		X															
VRC 610 AoU; Consent			X														
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; also wt at visit 02		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med history		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
[3,4]Product Administration				X													
Evening telephone safety check				X													
Begin 3-day Diary Card				X													
CBC / differential	EDTA	3		3		3			3	3		3					
ALT, AST, ALP, creatinine	GLT	4		4		4			4	4		4					
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT	X		X		X				X		X					
[5]Pregnancy test: urine or serum		X	X	X													X
[5]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X													X
HIV EIA (other tests, if needed)	SST	4							4								
HIV risk-reduction counseling		X		X					X								
HBcAb	SST	4															
HCV Ab	SST	4															
Research Samples																	
Timed PK samples	SST			4		4	4	4	4	4	4	4	4	4	4	4	4
PBMCs	EDTA	20															
Serum	SST	8	8	8			8	8	8	8	8	8	8	8	8	8	8
Daily Volume (mL)		**47**	**8**	**19**	**0**	**11**	**12**	**12**	**23**	**19**	**12**	**19**	**12**	**12**	**12**	**12**	**12**
Cumulative Volume (mL)		**47**	**55**	**74**	**74**	**85**	**97**	**109**	**132**	**151**	**163**	**182**	**194**	**206**	**218**	**230**	**242**

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

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

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

[3] All subjects will receive 10E8VLS. Subjects in Group 3 will also receive VRC07-523LS. Refer to Section 4.2.3 for SC administration instructions of two study products by anatomical site.

[4] The PK blood draw "visits," defined by hours after an injection, are relative to the exact time of the end of injection (EOI). The exact start and end times of product administration and the time of PK blood draw(s) are recorded to ensure accurate PK analysis. All subjects will be observed for 4 hours after each product administration.

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

Schedule 2: Repeat-dosing with 10E8VLS Alone (Group 2) or Concurrently with VRC07-523LS (Group 4)																							
Visit Number			01R	02	02A	03	04	05	06	07	09	10	11	11A	11E	12	13	14	15	16	17	17A	17E
Time After Injection				Pre D0	EOI D0	24hr	48hr	72hr	1wk	Wk2	Wk4	Wk8	Pre Wk12	EOI Wk12	24hr	72hr	Wk13	Wk14	Wk16	Wk20	Pre Wk24	EOI Wk24	24hr
[1]Day of Study			-42 to -1	D0	D0	D1	D2	D3	D7	D14	D28	D56	D84	D84	D85	D87	D91	D98	D112	D140	D168	D168	D169
Clinical	**Tube**	**Screen**	**Enroll**	**Day of injection**									**Day of injection**								**Day of injection**		
VRC 500 Screening Consent		X																					
VRC 610 AoU; Consent			X																				
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; wt at visits 02, 11, and 17		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med hx		X	X	X		X	X	X	X	X	X	X	X			X	X	X	X	X	X		
[3,4]Product Administration				X									X								X		
Evening telephone safety check				X									X								X		
Begin 3-day Diary Card				X									X								X		
Phone contact; clinic visit if indicated															X								X
CBC / diff	EDTA	3		3		3			3	3		3	3			3	3	3		3	3		
ALT, AST, ALP creatinine	GLT	4		4		4			4	4		4	4			4	4	4		4	4		
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT	X		X						X			X					X			X		
[5]Pregnancy test: urine or serum		X	X	X									X								X		
[5]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X									X								X		
HIV EIA (other tests, if needed)	SST	4							4								4						
HIV risk-reduction counseling		X		X					X				X				X				X		
HBcAb	SST	4																					
HCV Ab	SST	4																					
Research Samples																							
Timed PK samples	SST			4		4	4	4	4	4	4	4	4			4	4	4	4	4	4		
PBMC	EDTA	20																					
Serum	SST	8	8	8			8	8	8	8	8	8	8				8	8	8	8	8		
Daily Volume (mL)		**47**	**8**	**19**	**0**	**11**	**12**	**12**	**23**	**19**	**12**	**19**	**19**	**0**	**0**	**11**	**23**	**19**	**12**	**19**	**19**	**0**	**0**
Cumulative Volume (mL)		**47**	**55**	**74**	**74**	**85**	**97**	**109**	**132**	**151**	**163**	**182**	**201**	**201**	**201**	**212**	**235**	**254**	**266**	**285**	**304**	**304**	**304**

Visit windows: : Schedule Visits 02A through 11 with respect to day 0. Schedule Visits 11A through 17 with respect to Visit 11. Visit A (+10 min); Visit E (+ 1 day); Visits 03, 04, 05, 12, and 18 (± 6 hrs); Visits 06, 07, 13, and 14 (±2 days); Visits 09, 10, 11, 15, 16 and 17 (±7 days, with not less than 21 days between injections). Visits 08, 11B, 11C, 17B, and 17C are not applicable to Schedule 2.

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

[2] Screening includes physical exam with vital signs, height (ht) and weight (wt). At other visits, if medically indicated, a targeted exam is performed. Otherwise only blood pressure (BP) and temperature are required, except at Visits 02, 11, and 17 when weight is also obtained to use for ordering the study product, dosed based on "mg/kg".

[3] All subjects will receive 10E8VLS. Subjects in Group 4 will also receive VRC07-523LS. Refer to Section 4.2.3 for SC administration instructions of two study products.

[4] The PK blood draw "visits," defined by hours after an injection, are relative to the exact time of the end of injection (EOI). The exact start and end times of product administration and the time of PK blood draw(s) are recorded to ensure accurate PK analysis. All subjects will be observed for 4 hours after each product administration.

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

* The study schedule for subjects who discontinue product administration will be modified. Subjects who have received product administration 1 only will follow Schedule 2 through Visit 10, and then move to Schedule 3. Subjects who have received product administration 1 and 2 will follow Schedule 2 through Visit 16 and then move to Schedule 3.

Schedule 2(continued): Repeat-dosing with 10E8VLS (Group 2) or Concurrently with VRC07-523LS (Group 4)										
Visit Number*		18	19	20	21	22	23	24	25	26
Time After Injection		72hr	Wk25	Wk26	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
Day of Study		D171	D175	D182	D196	D224	D252	D280	D308	D336
Clinical	**Tube**									
Targeted physical exam, BP, pulse, temp		X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med hx		X	X	X	X	X	X	X	X	X
CBC / diff	EDTA	3	3	3		3				
ALT, AST, ALP, creatinine	GLT	4	4	4		4				
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT			X						
Pregnancy test: urine or serum										X
[2]Pregnancy prevention counseling / Reproductive Information Form										X
HIV EIA (other tests, if needed)	SST		4							
HIV risk-reduction counseling			X							
Research Samples										
Timed PK samples	SST	4	4	4	4	4	4	4	4	4
Serum	SST		8	8	8	8	8	8	8	8
Daily Volume (mL)		**11**	**23**	**19**	**12**	**19**	**12**	**12**	**12**	**12**
Cumulative Volume (mL)		**315**	**338**	**357**	**369**	**388**	**400**	**412**	**424**	**436**

Visit windows: Schedule Visits 17A through 26 with respect to Visit 17. Visit 18 (± 6 hrs), Visits 19-22 (±2 days), and Visits 23-26 (±7 days).

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

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

- Subjects who have received one product administration will follow Schedule 2 through Visit 10, and then move to Schedule 3.
- Subjects who have received two product administrations will follow Schedule 2 through Visit 16 and then move to Schedule 3.

Schedule 3: Groups 2 and 4 Discontinued from Further Product Administration								
Visit Number		11	15	16	17	21	22	23
Time After Injection		Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36
Day of Study		D84	D112	D140	D168	D196	D224	D252
Clinical	**Tube**							
Targeted exam, BP, pulse, temp		X	X	X	X	X	X	X
Interim med history		X	X	X	X	X	X	X
Pregnancy test: urine or serum			X		X			X
Pregnancy prevention counseling/ Reproductive Information Form			X		X			X
Research Samples								
PK samples	SST	4	4	4	4	4	4	4
Serum	SST	8	8	8	8	8	8	8
Daily Volume (mL)		**12**	**12**	**12**	**12**	**12**	**12**	**12**
Cumulative Volume (mL), One Product Administration Received		**194**	**206**	**218**	**230**			
Cumulative Volume (mL), Two Product Administrations Received					**297**	**309**	**321**	**333**

Visit windows: ±7 days for all visits shown.

Group 2 and 4 subjects who do not receive the 2nd and/or 3rd study product administrations will continue study participation under this modified schedule.

- If only one product administration was received, subjects will follow their originally assigned study schedule through Visit 10 and then move to Schedule 3 for Visits 11-17. The final study visit will be Visit 17 for these subjects.
- If two product administration were received, subjects will follow their originally assigned study schedule through Visit 16 and then move to Schedule 3 for Visits 17-23. The final study visit will be Visit 23 for these subjects.

APPENDIX III: TABLE FOR GRADING SEVERITY OF ADVERSE EVENTS

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from:

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

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

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

INSTITUTE: NIAID

STUDY NUMBER: 18-I-0113 PRINCIPAL INVESTIGATOR: Martin Gaudinski, MD

STUDY TITLE: VRC 610: A Phase I Safety and Pharmacokinetics Study to Evaluate a Human Monoclonal Antibody (MAB) VRC-HIVMAB095-00-AB (10E8VLS) Administered Alone or Concurrently with MAB VRC- HIVMAB075-00-AB (VRC07-523LS) Via Subcutaneous Injection in Healthy Adults

Initial Review Approved by the IRB on 06/07/18
Amendment Approved by the IRB on 09/05/18 (B) Date Posted to Web: 09/12/18
Standard, Version 2.0

INTRODUCTION

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

- Taking part in NIH research is entirely voluntary.
- You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.
- You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

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

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

PURPOSE AND PLAN OF THE STUDY

HIV infection is a serious disease with no cure or vaccine to prevent it. Researchers have been working hard to figure out new ways to treat and prevent HIV infection. The use of antibodies as a way to prevent or treat HIV infection appears promising. Antibodies are naturally made by the body to fight germs so that people remain healthy. This study will test two antibodies that were made artificially in the lab and may be able to prevent HIV infection. One is called 10E8VLS and the other is called VRC07-523LS. Both antibodies have been used in the lab to stop a virus like HIV from infecting animals. The antibodies are being studied because they may work better together to block HIV infection. The U.S. Food and Drug Administration (FDA) only allows these antibodies to be used for research because they are experimental products.

This study will be the first time 10E8VLS is tested alone and with VRC07-523LS in people. About 25 people have gotten VRC07-523LS in one research study. The antibodies will be given as an injection underneath your skin (subcutaneously, SC) in your belly, arm, or thigh. The goals of this study are to see if the antibodies are safe and well-tolerated and to see how long they stay in your blood. We will also check if your body makes a response to them.

About 16 to 30 people will take part in this study at the NIH Clinical Center in Bethesda, Maryland. You will need to complete about 13 to 26 clinic visits over 24 to 48 weeks depending on your study group.

STUDY PRODUCTS

The 10E8VLS and VRC07-523LS antibodies are monoclonal antibodies (MAbs) that target HIV. Monoclonal means that all of the 10E8VLS or VRC07-523LS antibodies are exactly the same. Part of 10E8VLS was discovered in a person with a chronic HIV infection. Part of VRC07-523LS was discovered in another HIV-infected person. Scientists at the NIH studied many antibodies made from these two people, and then figured out how to make them in the lab. They made changes to the antibodies so they stay in the body longer than usual. The 10E8VLS and VRC07-523LS MAbs are made with the same high standards that are required for medications normally prescribed to people.

We do not know if 10E8VLS or VRC07-523LS can prevent or treat HIV in humans when used alone or together. This study will not be able to answer that question. Other studies will have to be done. You should not assume any protection against HIV by participating in this research study.

You CANNOT get HIV from 10E8VLS or VRC07-523LS.

ELIGIBILITY

The screening process has shown that you may be eligible to take part in this study because you are:

- 18 to 60 years old.
- In general good health without major medical problems.
- Willing to get injections with one or both experimental antibodies.
- Willing to donate blood samples for future research.
- Willing to be tested for HIV infection.
- Willing to use birth control for the whole study if you are able to get pregnant.

STUDY PROCEDURES

The study will have 4 groups as shown in the Study Design table. Each group will have about 3 to 5 people in it. People in Group 1 will get 1 dose of 10E8VLS. People in Group 2 will get 3 doses of 10E8VLS. The third group will get 1 dose of 10E8VLS and 1 dose of VRC07-523LS. The fourth group will get 3 doses of 10E8VLS and VRC07-523LS. You will get each MAb dose injected under the skin and into the fatty tissue of your belly, upper arm, or upper thigh. You will be in the clinic for about 8 hours on the day each dose is given. Other clinic visits will take about 2 hours.

If you are assigned to Group 1 or 3, you will only get the assigned dose at 1 visit. This will let us see if the dose is safe and how long the antibodies will last in the body. You will need to complete about 13 clinic visits over 24 weeks if you are in this study group.

If you are assigned to Group 2 or 4, you will get the assigned dose at 3 visits. This will let us see how much of the antibodies stay in the body after three doses and if it is safe. You will need to complete about 26 clinic visits over 48 weeks. If you do not get all of the assigned doses, then you may have less study visits and complete the study sooner than 48 weeks.

Your body weight is used to calculate the amount of 10E8VLS and VRC07-523LS you will get. You will be weighed on each day the assigned dose will be given.

The dose groups are shown in the Study Design table.

Study Design

Group	Subjects	Study Product		Schedule		
		Dose	Antibody	Day 0	Week 12	Week 24
1	3	5 mg/kg	10E8VLS	X		
2	3	5 mg/kg	10E8VLS	X	X	X
3	5	5 mg/kg each	10E8VLS + VRC07-523LS	X		
4	5	5 mg/kg each	10E8VLS + VRC07-523LS	X	X	X
Total	**16**					

The study will open with Groups 1 and/or 2. If there are no safety concerns in these groups, then Groups 3 and 4 will begin to enroll subjects. People who can only take part in the study for 24 weeks may be enrolled into Group 1 or 3. People who can take part in the study for up to 48 weeks may be enrolled into any group.

A pregnancy test will be given to all women who are able to get pregnant each time the study product(s) is/are to be given. The result of the test must be negative in order to get the study product(s).

We will use a small needle to inject each MAb dose into the fatty tissue of your belly, upper arm, or upper thigh. You will get 1 to 4 injections at the same visit in different places on the body if you are assigned to Group 1 or 2. If you are assigned to Group 3 or 4, you will get 2 to 8 injections at the same visit in different sites on your body. We will monitor you for at least 4 hours after all of the injections are given and call you the evening of each injection visit to ask you how you are feeling. If you are in Group 2 or 4, we will also call you the day after your 2nd and 3rd injection visits. It is very important we speak to you and that you return any missed call so we know you are safe. We will collect blood samples from you before the injection and then at every scheduled follow-up visit.

We will give you a ruler and thermometer and ask you to check your temperature every day for 3 days after you get the study product(s). You will need to record your highest temperature and any symptoms you have. You will use the ruler to measure any redness, swelling, or bruising you may have at the injection site(s). You will get a password to a secure website to record this information. If you do not have a computer, smart phone, or tablet, you may use a paper diary instead.

You should tell a Vaccine Research Center nurse or doctor as soon as possible if you have any side effects after you get the study product(s). You can reach the staff by phone 24 hours a day, seven days a week. If you have symptoms, you may be asked to come into the clinic for a physical exam before your next scheduled visit. It is very important that you follow the instructions from the clinic staff.

Follow-up visits: We will check you for any health changes or problems at each visit. We will ask you how you are feeling and if you have taken any medications. We will draw about 1 to 5 tubes of blood at scheduled study visits. We will tell you right away if any of your test results show a health problem.

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

Clinical studies follow a set schedule. This helps us to 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. Comparing your sample results to others at the same time-point after all subjects receive the study products is very important to building our knowledge. You should try to not miss any visits.

HIV TESTING AND COUNSELING

HIV risk-reduction counseling will be provided to you if you take part in this study. We will tell you how to remain HIV-uninfected and give you prevention resources. We will also test you for HIV. If you are infected with HIV, you will not receive any more of the study product(s). We will tell you what the results mean, how to find care, how to avoid infecting others, how we report the infection, and the importance of informing your partners that may be at risk because of your HIV infection.

If you have questions about HIV testing, you should discuss them with the study nurse or doctor. You may also call an NIH Clinical Center HIV counselor at 301-496-2381.

MONITORING OF THE STUDY

A group of physicians and scientists at NIH will monitor safety in 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, further dosing with 10E8VLS or VRC07-523LS may be delayed or canceled.

GENETIC TESTING

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

The genetic testing performed in this study is for research purposes only. Any genetic information collected or learned about you will be kept confidential.

STORED SAMPLES

We will collect blood samples from you during the study. We will keep these samples until they are destroyed or used for future research to learn more about monoclonal antibodies, vaccines, the immune system, and other research questions. Results from research with your samples will not be in your medical record or reported to you.

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

Risks from Stored Samples: There is a risk of unplanned release of information from your medical records. The chance that this information will be given to an unauthorized person without your permission is very small. Possible problems with

the unplanned release of information include discrimination when applying for insurance and employment. Similar problems may occur if you give information about yourself or agree to have your medical records released.

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

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

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

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

HUMAN DATA SHARING

To advance science, it is helpful for researchers to share information they get from studying humans by putting it into shared scientific databases. Researchers can then study the information combined from many studies to learn even more about health and diseases.

If you agree to take part in this study, some of your data will be placed into one or more scientific databases. We will remove identifying information like your name and address, and then label it with a special code or number (for example, 5678123). The data may then be used for future research and shared broadly for research purposes. Only researchers who are approved to access the database may be able to see and use your information. You will not get any direct benefits from future research that uses your data and information.

You may stop participating in this study at any time and withdraw permission for your individual data, specimens, and health information to be used for additional or future research. You may ask to have your research data destroyed. However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

Your study records may also be shared with other US, local, and foreign regulatory bodies that approve new medicines.

POSSIBLE STUDY RISKS

Risks of 10E8VLS alone and with VRC07-523LS: This study is the first time that 10E8VLS alone and with VRC07-523LS will be given to people. There are several MAb medications that are used in people. Other similar products have been given safely into a vein (intravenously, IV). Local reactions at the site of SC injections are common, but are usually mild and go away in a few days. Most side effects tend to happen within the first 24 hours. Side effects to antibodies given by SC dosing may include mild pain at the site of injection; tiredness, muscle pain outside the injection site, and headache.

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

Anaphylaxis is one type of allergic reaction that may happen soon after an MAb product is given. This reaction can include

difficulty breathing, low blood pressure, hives, rash, or swelling in the mouth and face.

Serum sickness is a type of reaction that may happen several days or weeks after an MAb is given. This reaction may include hives, rash, fever, enlarged lymph nodes, muscle pains, or joint pains.

Some antibodies of the type that change how the immune system works can increase the risk of serious infections. Neither 10E8V6LS nor VRC07-523LS are expected to increase the risk of serious infections because they both attack a virus and do not target human cells.

Unknown risks: Both 10E8V6LS and VRC07-523LS may have other side effects that are not yet known. Participation in this study may affect your eligibility for future monoclonal antibody studies. We will give you any new information about risks or other information that may affect your decision to continue in the study as it becomes available.

You may not donate blood while taking part in this study and you may not donate blood for one year after the date of your last dose of 10E8V6LS or VRC07-523LS.

Risks of injections: It is possible that you may have some side effects. General risks of methods that use a needle include stinging, discomfort, pain, soreness, redness, bruising, swelling or a tiny cut at the needle insertion site.

Risks of Blood Drawing: Blood drawing may cause pain, bruising, and may cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken.

Risks during Pregnancy: We do not know what effects 10E8V6LS or VRC07-523LS may have on a fetus or nursing infant. You must notify the clinic staff right away if you get pregnant during this study or think that you might be pregnant. If you get pregnant, you will not receive any more doses of the study product(s) and we will not collect any more blood for research. However, you will be asked to continue with study follow-up visits to check on your health and to report the outcome of the pregnancy.

POSSIBLE BENEFITS

This study will not provide you with any direct health benefit. The 10E8VLS and VRC07-523LS antibodies are not proven to prevent HIV infection in people. What we learn from this study will help us understand more about using 10E8VLS and VRC07-523LS in humans.

COSTS TO YOU FOR 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.

COMPENSATION TO YOU FOR YOUR PARTICIPATION

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

Total compensation for completion of the study is estimated to be between $2500 to $4700 and is based on the number and type of study visits you complete. You will get:

- $175 for scheduled visits with a blood draw.

- $75 for clinic visits that do not include a blood draw.
- $325 for SC product administration visit(s).
- $25 total for timely completion of all 3 days of an electronic diary.

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

REASONS FOR STOPPING YOU FROM GETTING MORE DOSES OF STUDY PRODUCT ADMINISTRATION OR REMOVING YOU FROM THE STUDY

You may be stopped from getting the study product(s) for several reasons, including:

- You don't keep appointments or follow study procedures.
- You get a serious illness that needs ongoing medical care.
- You have a serious side effect thought to be due to 10E8V6LS and/or VRC07-523LS.
- You enroll in another research study at the same time you are in this study.
- You become pregnant.
- The study is stopped or canceled.

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

You may choose to stop participating in the study at any time. If you received any doses of 10E8V6LS or VRC07-523LS, you will be asked to keep follow-up visits so we can monitor your health. We may stop collecting samples that are for research purposes only.

ALTERNATIVES

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

NEW FINDINGS

We will give you any new information about risks or other information that may affect your decision to continue in the study as this information becomes available.

CONFLICT OF INTEREST

The NIH research staff is checked yearly for conflicts of interest. You may ask the research team for more information or for a copy of the NIH Guide to Avoiding Financial or Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research. This study may have investigators who are not NIH employees. Non-NIH investigators are expected to follow the principles of this guide but are not required to report their personal financial holdings to the NIH.

The NIH, including some members of the VRC scientific staff, developed the study products being used in this research study. The results of this study could play a role in whether the FDA or other regulatory agency will approve the study

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

CLINICALTRIALS.GOV

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

OTHER PERTINENT INFORMATION

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

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

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

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

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

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

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____

INSTITUTE: NIAID

STUDY NUMBER: 18-I-0113 PRINCIPAL INVESTIGATOR: Martin Gaudinski, MD

STUDY TITLE: VRC 610: A Phase I Safety and Pharmacokinetics Study to Evaluate a Human Monoclonal Antibody (MAB) VRC-HIVMAB095-00-AB (10E8VLS) Administered Alone or Concurrently with MAB VRC- HIVMAB075-00-AB (VRC07-523LS) Via Subcutaneous Injection in Healthy Adults

Initial Review Approved by the IRB on 06/07/18
Amendment Approved by the IRB on 09/05/18 (B) Date Posted to Web: 09/12/18
Supplemental, Version 2.0

Supplementary consent for an extended genetic testing (optional)

You agreed to participate in VRC 610 study for testing of two investigational human monoclonal antibodies to the HIV-1 envelope. This additional consent covers optional extended genetic testing that you may agree to. If you do not agree to this additional testing, you still can participate in the VRC 610 study.

There is a new type of genetic test that lets us look at the expressions of genes, called transcriptome sequencing. This test lets us look at the genes that are actively expressed at any given moment. However, it does not measure the amount of protein produced. Also, this new genetic test is still in development and researchers are working on understanding the data and how that data can be used in various clinical applications, such as in medicine to help prevent disease.

This test may take a long time to understand, and we may not have any news to give you about it. Since we are looking for genes that control infection or immune response, we will not report to you or your doctors things that we find that are not related to infection or immunity. However, if we find something in your DNA that we think is urgent to deal with because of your health, we will confirm the result and then tell you about it. We think this sort of problem will be rare.

Genetic Data Sharing

Following genetic testing for transcriptome sequencing, your sequence data **may** be shared in a controlled access public database, for other investigators to benefit from it. However, no personal, identifiable information will be shared in this process, as the shared results will be coded with no link back to you.

OTHER PERTINENT INFORMATION

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

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

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. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study or about any research-related injury, contact the Principal Investigator, Martin Gaudinski, MD or the Study Coordinator, [redacted] at [redacted]. You may also call the Clinical Center Patient Representative at [redacted].

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

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____