Protocol Title: VRC 611 (20I0096): A Phase I Safety and Pharmacokinetic Study to Evaluate a Human Monoclonal Antibody (mAb) VRC-HIVMAB0102-00-AB (CAP256V2LS) Administered via Subcutaneous and Intravenous Injection in Healthy Adults

NCT: 04408963

Documents:

- IRB-approved Protocol (v3.0 07OCT2022) - Statistical Analysis Considerations located in Section 6 of the Protocol
- IRB-approved Main Informed Consent (v3.0 07OCT2022) IRB Approval/Document Date: 07NOV2022

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VACCINE RESEARCH CENTER

PROTOCOL VRC 611
(NIH 20-I-0096)

Title: A PHASE I SAFETY AND PHARMACOKINETICS STUDY TO EVALUATE A HUMAN MONOCLONAL ANTIBODY (MAB) VRC-HIVMAB0102-00-AB (CAP256V2LS) ADMINISTERED VIA SUBCUTANEOUS AND INTRAVENOUS INJECTION IN HEALTHY ADULTS

Abbreviated Title: A Phase I Trial to Evaluate CAP256V2LS in Healthy Adults

IND Sponsor

Vaccine Research Center (VRC)

National Institute of Allergy and Infectious Diseases (NIAID)

Bethesda, Maryland, US

IND 147774

Investigational Product CAP256V2LS Manufacturer:

Manufactured for VRC by Leidos Biomedical Research, Inc., Frederick, MD

NIH Principal Investigator:

Richard Wu, M.D.
NIH, NIAID, VRC
[redacted]

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ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AIDS	Acquired immunodeficiency syndrome
AE	Adverse event
ART	Antiretroviral therapy
AoU	Assessment of Understanding
AUC	Area Under the Curve
bNAbs	Broadly-neutralizing human monoclonal antibodies
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CAPRISA	The Centre for the AIDS Programme of Research in South Africa
CBC	Complete blood count
cGMP	Current Good Manufacturing Practices
CMP	Clinical Monitoring Plan
CTP	Clinical Trials Program
DNA	Deoxyribonucleic Acid
EKG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ENV	Envelope
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HGH	Human Growth Hormone
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
LIMS	Laboratory Management Information System
mAb	Monoclonal Antibody
MedDRA	Medical dictionary for regulatory activities
MO	Medical Officer
NAT	Nucleic acid test
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH CC	NIH Clinical Center
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PI	Principal Investigator

PK	Pharmacokinetics
PSRT	Protocol Safety Review Team
QA	Quality Assurance
RBC	Red blood cells
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SC	Subcutaneous
SUSAR	Serious and unexpected suspected adverse reaction
U.S.	United States
ULN	Upper limit of normal
UPnonAE	Unexpected Problem that is not an Adverse Event
VCMP	Vaccine Clinical Materials Program
VEC	Vaccine Evaluation Clinic
VIP	Vaccine Immunology Program
VRC	Vaccine Research Center
WBC	White blood cells
WHO	World Health Organization

PROTOCOL SIGNATURE PAGE

VRC 611: A Phase I Safety and Pharmacokinetics Study to Evaluate a Human Monoclonal Antibody (mAb) VRC-HIVMAB0102-00-AB (CAP256V2LS) Administered Via Subcutaneous and Intravenous Injection in Healthy Adults

I, the Principal Investigator for the study site indicated above, agree to conduct the study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct the study in compliance with United States (US) Health and Human Services (HHS) regulations (45CFR 46); applicable US Food and Drug Administration (FDA) regulations; standards of the International Council for Harmonization Guidelines for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee (IRB/EC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health) and institutional policies. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation pertaining to the conduct of this study, including, but not limited to, case report forms, source documents, laboratory test results, and medication inventory records, per FDA regulation (21 CFR 312.62) and all applicable requirements. The protocol signature page will be signed for subsequent protocol approvals. No study records will be destroyed without prior authorization from VRC/NIAID.

Publication of the results of this study will be governed by the VRC/NIAID policies. Any presentation, abstract, or manuscript will be made available by the investigators to VRC Leadership for review prior to submission. I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Richard Wu, MD Name/Title of Principal Investigator	VRC / Vaccine Evaluation Clinic Investigator Study Site Name
_____ Signature of Principal Investigator	_____ Date

PRECIS

Title: **VRC 611**: A Phase 1 Safety and Pharmacokinetic Study to Evaluate a Human Monoclonal Antibody (mAb) VRC-HIVMAB0102-00-AB (CAP256V2LS) Administered Via Subcutaneous and Intravenous Injection in Healthy Adults.

Design: This open-label study will evaluate CAP256V2LS (VRC-HIVMAB0102-00-AB) in healthy adults. The primary hypothesis is that subcutaneous (SC) and intravenous (IV) administrations of CAP256V2LS will be safe and well-tolerated in healthy adults. A secondary hypothesis is that CAP256V2LS will be detectable in human sera with a definable half-life.

Study Product: The CAP256V2LS broadly neutralizing monoclonal antibody (bNAb) targets the V1V2 region of the HIV-1 envelope, is human in origin, and contains two amino acid modifications within the C-terminus of the heavy chain constant region designed to improve antibody half-life *in vivo*. This bNAb was developed by the VRC/NIAID/NIH in collaboration with The Centre for the AIDS Programme of Research in South Africa (CAPRISA) and is 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 CAP256V2LS drug product is supplied at a concentration of 100 mg/mL in a sterile, aqueous, buffered solution of 6.25 mL in single-use 10 mL glass vials.

R-Gene® 10 will be added as a stabilizing agent to IV doses of CAP256V2LS. R-Gene 10 (Arginine Hydrochloride Injection, USP) for intravenous infusion contains L-Arginine Hydrochloride, USP in Water for Injection (equivalent to a 10% solution).

Subjects: Healthy subjects, 18-60 years of age

Study Plan: This open-label study will include 2 dosing regimens with CAP256V2LS administered at 5 mg/kg IV and 5 mg/kg SC. A single dose of the study product will be administered on Day 0 as shown below.

VRC 611 Study Design

Groups	Study Product	Subjects per Group	Dose (mg/kg) and Route Administered	Day 0
1	CAP256V2LS	5	5 mg/kg IV	X
2	CAP256V2LS	5	5 mg/kg SC	X
	Total Subjects [1]	10		
[1] Enrollment up to 20 subjects is permitted in case additional evaluations for safety or pharmacokinetic (PK) evaluations are needed.				

Duration: Study participation will be approximately 24 weeks from the Day 0 product administration.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY RATIONALE

1.1.1 Rationale for Development of CAP256V2LS

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 2018 report by the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 74.9 million people have been infected with HIV since the start of the epidemic, contributing to 32 million deaths from AIDS-related illnesses[1]. Despite these statistics, global incidences of new infections have actually declined from peak rates in the mid-1990's; 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, also called V1V2 apex (PG9[10, 11], PGDM1400 [9], CAP256.25[12]). The VRC/NIAID is investigating clinical applications of these bNAbs[4, 6, 13, 14].

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) team in collaboration with the VRC isolated a family of 33 mAbs with broad HIV-1 serum neutralizing activity from a participant enrolled in the CAPRISA 002 acute HIV infection study[12, 15]. While these antibodies demonstrated robust neutralization potential against diverse HIV subtypes across the world, CAP256-VRC26.25 was found to be extremely potent and capable of neutralizing 71% of HIV-1 subtype C viruses, the dominant subtype in South Africa. CAP256-VRC26.25 was isolated at the VRC [12] and subsequently modified to incorporate the LS mutation resulting in increased recirculation of functional IgG and higher plasma half-life[16, 17]. In addition, a single amino acid change, lysine to alanine, was made in the CDRH3 region to improve manufacturability without altering neutralization breadth or potency. The variant with these changes was named CAP256V2LS. The high potency, breadth in Clade C and long half-life of the CAP256V2LS mAb make it an excellent candidate for further development for HIV prevention alone and/or in combination with other mAbs[18-22]. This Phase I study will investigate the safety and pharmacokinetics (PK) of CAP256V2LS in healthy adults.

1.2 BACKGROUND

1.2.1 Rationale for Study Design

The proposed 5mg/kg dose of CAP256V2LS administered via IV or SC route has been previously assessed in other Phase 1 trials in healthy adults for other VRC manufactured human bNAbs such as VRC01, VRC01LS, VRC07-523LS [17, 23-25]. Administration by IV and SC routes at the 5 mg/kg dose of these mAbs overall have been assessed as generally well tolerated, with no deaths or serious adverse events that were ultimately determined to be related to the study product by the Sponsor.

R-Gene® 10 (Arginine Hydrochloride Injection, USP) will be added as a stabilizing agent to IV doses of CAP256V2LS. R-Gene 10 was developed by Pfizer and is indicated as an intravenous stimulant to the pituitary for the release of human growth hormone (HGH) in patients where the measurement of pituitary reserve for HGH can be of diagnostic usefulness. Arginine has been included in the formulation buffer for previous VRC bNAbs and is also included in the formulation buffer for CAP256V2LS. Arginine in the form of R-Gene 10 is being further added during pharmacy preparation for IV doses of CAP256V2LS to compensate for dilution during preparation and maintain an adequate concentration of Arginine to stabilize the final product.

1.2.2 Previous Human Experience with CAP256V2LS

The first-in-human evaluation of CAP256V2LS as an investigational drug commenced in the South African trial CAPRISA 012B under the South African Health Products Regulatory Authority (SAHPRA). As of 23 August 2021, 42 HIV-negative participants have been enrolled into the CAPRISA 012B study and have received one intravenous or subcutaneous injection of CAP256V2LS. Overall, reported reactogenicity events ranged from mild to severe and all reactogenicity events resolved within the three-day reactogenicity assessment period. All reactogenicity events attributed to study injection had resolved. No infusion reactions occurred during or after study product administration during a one hour observation period.

There were 76 unsolicited adverse events reported in 37 out of 42 (88%) participants, of which 50 events were attributed as related to study product. Transient lymphocytopenia was a common event observed in 8 participants, of which 2 were mild (Grade 1 range, 600 to <650 cells/mm^3) , 2 were moderate (Grade 2 range, 500 to <600 cells/mm^3), 2 events were severe (Grade 3 range, 350 to <500 cells/mm^3), and 2 were graded potentially life threatening (Grade 4 range, <350 cells/mm^3). These events occurred at day 1 post study product administration and resolved by day 3 to day 7 with no clinical sequalae. After DSMB review of the data and consultation with expert hematologists, the DSMB concluded that this transient lymphocytopenia was not a safety concern, and recommended informing subjects of the potential risk of lymphocytopenia and further investigating the transient lymphocytopenia should it occur in future participants.

No SAEs or adverse events resulted in study product discontinuation in any participant. No suspected unexpected serious adverse reactions (SUSAR) have been reported to SAHPRA. Refer to the CAP256V2LS Investigator's Brochure for additional information.

Enrollment in this study, VRC 611, has been completed as of June 13th, 2022, with 10 participants enrolled. All subjects received the product as per protocol.

Local Reactogenicity

Of the ten participants enrolled in this study, four (40%) reported a local solicited adverse event. All four of these participants were in the SC group. Two (20%) subjects reported mild severity and two (20%) reported moderate severity symptoms. The most common local symptom was redness at the injection site, with one (10%) participant reporting mild and two (20%) reporting moderate severity. One (10%) participant reported moderate swelling. One AE of mild pruritis and one AE of mild pain at the injection site were also reported.

Systemic Reactogenicity

Of the 10 participants, 9 (90%) reported at least one or more systemic solicited AE with the maximum severity being severe for 1 (10%) participant, moderate for 7 (70%) participants, and mild for 1 (10%) participant. The most common adverse events were malaise and muscle aches, each reported by 9 (90%) participants with 1 participant (10%) reporting severe, 5 (50%) moderate, and 3 (30%) mild AEs. Chills were also reported by 9 (90%) participants, with 1 participant (10%) reporting severe, 4 (40%) moderate, and 4 (40%) mild AEs. Headaches were reported by 8 (80%) participants, 6 (60%) were moderate and 2 (20%) were mild in severity. An elevated temperature was reported by 7 (70%) participants, 5 (50%) moderate and 2 (20%) mild in severity. Joint pain was reported by 6 (60%) of participants, 2 (20%) moderate and 4 (40%) mild in severity. Nausea was reported by 3 (30%) participants, 2 (20%) moderate and 1 (10%) mild in severity.

All solicited reactogenicity symptoms resolved within the 7-day reactogenicity collection period without residual effects.

Unsolicited Adverse Events

Eight (8/10, 80%) participants experienced one or more unsolicited adverse events. The maximum severity was potentially life-threatening for 1 (10%) participant, severe for six (60%), and moderate for 1 (10%) participant. No SAEs or study pauses occurred.

The most common unsolicted adverse event was lymphopenia in 8 (80%) participants, 5 in IV and 3 in SC participants, including 1 (10%) potentially life-threatening, 6 (60%) severe, and 1 (10%) mild, all of which were evaluated as related to study product. Grade 4 lymphopenia occurred in a Group 2 subject (5 mg/kg, SC) 1 day post product administration and resolved in 6 days. All AEs of lymphopenia were asymptomatic and resolved without residual effects.
One (1/10, 10%) participant had moderate dyspepsia, 1 (10%) had moderate AE of elevated liver transaminases, 1 (10%) had mild abdominal pain, 1 (10%) had mild hypertension; these were evaluated as related to study product and resolved without residual effects.

Unrelated adverse events included 1 mild AE of hypotension, 1 mild AE of hypertension, and 1 moderate AE of upper respiratory infection. These resolved without residual effects.

1.3 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, ex vivo analysis to assess the neutralization activity of CAP256V2LS post-injection/infusion, and evaluation for anti-drug antibody (ADA) development following product exposure. Other assays may also be completed from stored samples at a later date if additional assessments are needed.

The VRC's Vaccine Immunology Program (VIP), Gaithersburg, MD, will process blood and store coded samples, and will either perform sample testing or ship coded samples to designated research laboratories at the VRC or other approved collaborators. Some immunogenicity assays may be performed by VRC laboratories in Bethesda, MD, or by approved contract laboratories or research collaborators. See Appendix I for schedules, volumes and tube types to be used for research sample collection. Tube types for clinical laboratory evaluations and research collections are selected according to institutional requirements and are shown in the Schedule of Evaluations to estimate blood volumes. Different tubes may be used to meet site requirements. Samples will be transported according to approved site procedures.

1.3.1 Pharmacokinetic (PK) Analysis

Concentrations of CAP256V2LS will be measured by similar methodologies as previously described for other VRC mAb products[24].

1.3.2 HIV Pseudovirus Neutralization

Subject sera collected (but not limited to) at baseline (Day 0), 48 hours post-administration and at Day 168 may be evaluated to assess the functional capacity of passively administered CAP256V2LS to neutralize pseudotyped HIV viruses using an in vitro cell-based virus neutralization assay as described previously for VRC01, VRC01LS, and VRC07-523LS[6, 23-26]

1.3.3 Detection of Anti-Drug Antibody

Assays for detection of ADA will be performed at specified timepoints following product administration compared to baseline status using a similar methodology as previously described for other VRC mAb products[24]. Additional timepoints may be assessed per PI discretion if clinically relevant.

1.3.4 Allotype-Specific Effects

Exploratory evaluation to detect for theoretical immunoglobulin G1 (IgG1) allotype-specific effects may be performed in cases when PK measures suggest a reduced CAP256V2LS antibody half-life or an ADA response [27-29]. Coded stored samples may be used for evaluation of the genetic sequence of the immunoglobin heavy chain constant region allotype.

2 STUDY PRODUCT

2.1 CAP256V2LS

VRC-HIVMAB0102-00-AB (CAP256V2LS) was developed by the VRC, NIAID, NIH in collaboration with CAPRISA. The study product was manufactured for the VRC under current Good Manufacturing Practice (cGMP) by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc., Frederick, MD.

R-Gene 10 (Arginine Hydrochloride, Injection, USP) will be added as a stabilizing agent to IV doses of CAP256V2LS. R-Gene 10 for IV injection was developed by Pfizer. Each 100 mL of R-Gene 10 contains 10g of L-Arginine Hydrochloride, USP in Water for Injection (equivalent to a 10% solution).

2.2 NONCLINICAL STUDIES

To assess the IC_{50} and IC_{80} of CAP256V2LS and parental mAb, CAP256-VRC26.25, the standard multiclade 208 Env-pseudovirus panel was used[30]. The 208 pseudovirus panel includes the major circulating HIV-1 genetic clades and viruses derived from acute and chronic stages HIV-1 infection. Within the 208 pseudoviruses tested, 58 are Clade C, the dominant clade in southern Africa. The CAP256-VRC26.25 material used in this assay was produced in HEK/293expi cells. The CAP256V2LS material was produced in stably transfected CHO cells using processes representative of the manufacturing methods used for the GMP drug product.

CAP256V2LS was slightly broader and more potent than the parental CAP256-VRC26.25, with CAP256V2LS neutralizing 63% of the pseudoviruses with a median IC_{50} of 0.001 ug/mL and CAP256-VRC26.25 neutralizing 59% of the pseudoviruses with a median IC_{50} of 0.006 ug/mL. CAP256V2LS is particularly broad and potent in Clade C by neutralizing 72% of the pseudoviruses with a median IC_{50} of 0.001 ug/mL.

The polyspecificity of CAP256V2LS was assessed by analyzing its reactivity with HEp-2 cells by immunohistochemistry and its binding to cardiolipin by ELISA . VRC01LS and 4E10 were used as negative and positive controls respectively. CAP256V2LS displayed no reactivity with a score of 0 for binding to HEp-2 cells at 25 ug/mL. CAP256V2LS showed higher binding to cardiolipin than VRC01LS but was much lower than 4E10 which binds strongly to cardiolipin and has been administered to people in multi-dose phase I and II trials without any serious adverse reactions[18, 31]. Assessment of anti-phospholipid characteristics by impact on activated partial thromboplastin time (aPTT) was performed using methods previously described[32]. CAP256V2LS samples did not exhibit lengthening aPTT. The results demonstrated that CAP256V2LS does not have anti-phospholipid characteristics.

The VRC evaluated the *in vivo* pharmacokinetic profile of CAP256V2LS, produced from a stably transfected CHO cell line in human FcRn transgenic mice and rhesus macaques. Mice received a single 5 mg/kg IV dose and the levels of antibody in the sera were evaluated at various timepoints up to 56 days after product administration were then quantified by an anti-CAP256V2LS idiotype based ELISA method. The sera levels of CAP256V2LS were maintained about 1 ug/mL up to day 21 post infusion in most animals. The sera levels of the antibody decreased slowly over time reaching levels below detection limit starting at day 42 post infusion. The average half-life was calculated to be 7.7 days with a range of 6.2 to 8.5 days. The average AUC (Area Under the Curve) was calculated to be 126 Day ug/mL with a range of

102 to 151 Day ug/mL. The average clearance was calculated to be 40.25 mL/Day/kg with a range of 32.9 to 48.9 mL/Day/kg.

A single 10 mg/kg dose of CAP256V2LS was given to rhesus macaques via the SC (n=3) or IV (n=3) routes. The levels of antibody in the sera of these animals at various timepoints up to 56 days after administration were then quantified by an anti-CAP256V2LS idiotype based ELISA method. The initial sera antibody levels were higher when the antibody was given IV compared to SC, but by day 2 the sera antibody levels were similar in all animals irrespective of route of administration and followed similar distribution over time. Also, sera antibody levels were maintained above 10 ug/mL for up to 14 days post infusion in all animals irrespective of route. The average half-life for CAP256V2LS was calculated to be 14.3 days for the IV route and 9.9 days for the SC route, with a range of 5.8 days to 21.7 days with the half-lives slightly higher for the IV route. The AUC was a bit higher for the IV route (616 Day ug/mL) compared to the SC route (514 Day ug/mL) due to the higher initial peak observed in the sera levels for the IV route compare to the SC route. The clearance was similar between the two routes (15.87 mL/Day/kg for IV vs. 19.42 mL/Day/kg for SC).

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To evaluate the safety and tolerability of a 5mg/kg IV dose of CAP256V2LS administered once in healthy adults
- To evaluate the safety and tolerability of a 5mg/kg SC dose of CAP256V2LS administered once in healthy adults

3.2 SECONDARY OBJECTIVES

- To evaluate the pharmacokinetics of CAP256V2LS through 24 weeks from product administration

3.3 EXPLORATORY OBJECTIVES

- To determine whether anti-drug antibody (ADA) to CAP256V2LS can be detected in sera of recipients at specific timepoints throughout the study
- To assess for IgG1 allotypes and allotype-specific effects on CAP256V2LS pharmacokinetics
- To explore and characterize the humoral and cellular response to CAP256V2LS

4 STUDY DESIGN AND CLINICAL PROCEDURES

This Phase 1 open-label study will be conducted at the VRC Vaccine Evaluation Clinic (VEC) in the NIH Clinical Center (NIH CC). The primary hypothesis is that CAP256V2LS will be safe and tolerable when administered by IV and SC routes. The secondary hypothesis is that CAP256V2LS will be detectable in human sera with a definable half-life.

Enrollment will begin in the 5 mg/kg IV group (Group 1) with no more than one subject per day for the first three participants to receive CAP256V2LS. Absent safety data that meet pause criteria, after 3 subjects have received 5 mg/kg IV in Group 1, enrollments into Group 2 may proceed. Any subject who receives the study product will be expected to follow the product administration schedule, also referred to as the Schedule of Evaluations (Appendix I), for a complete safety and research evaluation through study duration. The overall study schema is as follows:

Table 1: Study Schema

Groups	Study Product(s)	Subjects per Group	Dose (mg/kg) and Route Administered	Day 0
1	CAP256V2LS	5	5 mg/kg IV	X
2	CAP256V2LS	5	5 mg/kg SC	X
Total Subjects[1]		10		
[1] Enrollment up to 20 subjects is permitted in case additional evaluations for safety or pharmacokinetic (PK) evaluations are needed.				

4.1 STUDY POPULATION

All inclusion and exclusion criteria must be evaluated for eligibility.

4.2 INCLUSION CRITERIA

A subject must meet all of the following criteria to be included:

1. Able and willing to complete the informed consent process
2. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process
3. Available for clinical follow-up through the last study visit
4. 18 to 60 years of age
5. Based on medical history and physical examination, in good health and without clinically significant findings within 84 days prior to enrollment.
6. Weight ≤ 115 kg
7. Willing to have blood samples collected, stored indefinitely, and used for research purposes

Laboratory Criteria within 84 days prior to enrollment:

8. White Blood Cell (WBC) 2,500-12,000/mm3
9. WBC differential either within institutional normal range or accompanied by the

Principal Investigator (PI) or designee approval

10. Platelets = 125,000 – 500,000/mm3
11. Hemoglobin within institutional normal range or accompanied by the PI or designee approval
12. Creatinine ≤ 1.1 x upper limit of normal (ULN) based on the institutional normal range
13. Alanine aminotransferase (ALT) ≤1.25 x ULN based on the institutional normal range
14. Negative for HIV infection by an FDA approved method of detection

Criteria Specific to Women of Childbearing Potential:

15. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test (urine or serum) on day of enrollment, and prior to product administration
16. Agrees to use an effective means of birth control from at least 21 days prior to enrollment through the duration of study participation

4.3 EXCLUSION CRITERIA

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

1. Woman who is breast-feeding or planning to become pregnant during study participation
2. Any history of a severe allergic reaction with generalized urticaria, angioedema or anaphylaxis prior to enrollment that has a reasonable risk of recurrence during the study
3. Hypertension that is not well controlled
4. Receipt of any investigational study product within 28 days prior to enrollment. Note: SARS-CoV-2 vaccines approved by emergency use authorization are not exclusionary.
5. Receipt of any live attenuated vaccines within 28 days prior to enrollment.
6. Receipt of any vaccine within 2 weeks prior to enrollment/product administration
7. Prior receipt of a licensed or investigational monoclonal antibody
8. Prior receipt of an HIV vaccine
9. Any medical, psychiatric, social condition, occupational reason or other responsibility that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a subject's ability to give informed consent.

4.4 INCLUSION OF VULNERABLE SUBJECTS

4.4.1 Children

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

4.4.2 Adult Subjects who Lack Capacity to Consent

Adults who are unable to provide initial informed consent are excluded to enroll. Also, adults who permanently lose the capacity to provide on-going consent after initial consent and during the study will be discontinued from protocol participation as it is described in Section 4.4

4.4.3 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 CC and NIAID policies. For NIH employee subjects, consent will be obtained by an individual who is independent of the employee's team. If an NIH staff member seeks to enroll in research taking place within their own work unit or conducted by any of their supervisors, the employee will be:

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

- When possible, consent should be obtained by an individual in a non-supervisory relationship with the subject, and

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

4.5 CLINICAL PROCEDURES AND EVALUATIONS

Evaluation of study product safety will include laboratory studies, medical history, physical assessment by clinicians, and subject self-assessment on a diary card for 7 days after product administration. The study schedule is presented in the Schedule of Evaluations, Appendix I. Total blood volume drawn from each subject will not exceed the NIH Clinical Center Guidelines.

4.5.1 Recruitment and Retention Strategies

Study enrollments will be conducted at the NIH Clinical Center. Study subjects will be recruited through the VRC's screening protocol, VRC 500 (NCT 01375530). The on-site and off-site Institutional Review Board (IRB)-approved advertising will be implemented. Per a recruitment plan described in the VRC 500 protocol, efforts will be made to include women and minorities in proportions similar to that of the community from which they are recruited.

4.5.2 Costs

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

4.5.3 Compensation

Subjects will be compensated for time and inconvenience in accordance with the standards for compensation of the Clinical Research Volunteer Program. The compensation is $430 for a clinic visit that includes study product administration. If enrollment occurs on a different day than the study product administration visit, the compensation will be $200. Compensation will be $200 for scheduled follow-up visits that include a blood draw, $85 for clinic visits that do not include a blood draw or procedure, and $25 total for timely completion of all seven days of the electronic diary card.

4.5.4 Screening

All screening procedures for this study are described and will be completed through the VRC's screening protocol, VRC 500 (NIH 11-I-0164) used for all VRC IND studies conducted at the NIH Clinical Center. The Recruitment Plan per NIH Policy 302 for all VRC studies can be found in the NIH IRB approved VRC 500 protocol. Subjects will be recruited through Institutional Review Board (IRB)-approved advertising. Screening evaluations are performed to confirm eligibility and will include medical history review, physical exam, and the clinical laboratory tests detailed in the Schedule of Evaluations, Appendix I. Women presumed to be of reproductive potential will be given a pregnancy test. No screening procedures will be done under protocol VRC 611.

Additional health assessments may be conducted at screening based on clinical judgment. Screening evaluations for specific eligibility criteria (Section 4.1) must be completed within the time interval specified prior to enrollment for the given parameter and may be repeated, as needed, to confirm eligibility. Research blood samples will be collected anytime during screening through enrollment and will not be subject to the "84 days prior to enrollment" restriction.

The informed consent form (ICF) will be reviewed during screening. Counseling related to potential risks of the study product, pregnancy prevention, and avoiding exposure to HIV will be performed. An Assessment of Understanding (AoU) will be completed in association with

enrollment into VRC 611. Records will be kept documenting the reason that screened subjects do not enroll.

4.5.5 Study Schedule

The Schedule of Evaluations in Appendix I provides details on the study schedule, the permitted windows for completing the visits, and the evaluations to be performed at each visit. The visit schedule is based on intervals of time after product administration. The clinicians will discuss the target dates and timing of product administration and sample collections with each subject before completing enrollment to help ensure that subjects can comply with the projected schedule.

4.5.6 Enrollment and Study Day 0

Enrollment is defined as the assignment of a study identification number in the clinical database. A clinician will discuss the target dates and timing of the study product administration and sample collections before completing an enrollment to help ensure that the subject can comply with the projected schedule. The group assignment is known to the staff and subject before enrollment into the study electronic database on Day 0.

Day 0 is defined as the day of CAP256V2LS 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). Day 0 evaluations and medical history prior to product administration are the baseline for subsequent safety assessments.

The study will start with subject enrollment into Group 1.

4.5.7 Product Administration

Product administration will be completed according to the assigned group. On the day of product administration (before CAP256V2LS is administered), study subjects will be clinically evaluated, and samples will be collected as per the Schedule of Evaluations (Appendix I). A subject who arrives at the clinic with fever or evidence of an acute illness that precludes product administration may be rescheduled within the allowed study visit window.

Pregnancy test results for women of childbearing potential must have a negative result to proceed with product administration.

If a subject is assigned to the IV administration group, the IV access will be placed in an arm vein in an aseptic manner. A different site may be used for collection of PK blood samples; however, the same site may be used after flushing the line if another site is not available. CAP256V2LS combined with R-Gene 10 as a stabilizing agent will be administered with approximately 100 mL of normal saline IV over about 30 minutes. Infusions lasting longer than 30 minutes are allowed. If the subject experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms.

If a subject is assigned to the SC administration group, the SC administration site(s) to be used must be assessed as acceptable by the clinician and the subject. The preferred SC administration site is the abdomen, but the upper arm or thigh may be used. Given the weight criterion in this study, the maximum volume needed to administer a 5 mg/kg SC dose is not expected to exceed

5.75 mL. The SC dose will be administered by standard needle in a maximum volume of about 2.5 mL per injection site. Up to 4 SC injection sites may be used if deemed necessary by the clinician. SC administration sites should be at least 2 inches apart.

Procedures for CAP256V2LS preparation and administration are described in Section 7.

4.5.8 Post-Product Administration Follow-up

All subjects will be observed for at least 2 hours following completion of product administration. Collection of PK samples will be conducted according to the Schedule of Evaluations for the subject's study group.

Prior to discharge from the clinic, subjects will be assessed for local and systemic reactogenicity and vital signs will be recorded. Any subject who is assessed as being unwell or has ongoing reactogenicity symptoms will be asked to remain in the clinic until evaluation and discharge by a study clinician. This includes the possibility of an overnight inpatient stay to evaluate for safety.

In keeping with the NIH CC policy and good medical practice, acute medical care will be provided to subjects for any immediate allergic reactions or other injury resulting from participation in this research study.

4.5.9 Solicited Adverse Events (Reactogenicity)

Subjects will be given a "diary card" (paper and electronic-based diary is available), a thermometer, and a measuring device. Subjects will use the diary to record their highest temperature, local and systemic symptoms, and concomitant medications daily for 7 days after product administration. Subjects will be provided training on diary completion and proper usage of the thermometer to measure temperature and the measuring device to measure product administration site symptoms. Completion of diary training will be noted in the source documents. While the electronic diary is preferred, subjects will have the option to use a paper diary. The paper diary, if used, will be transcribed into the study database and stored in the subject file for monitoring purposes. When neither paper nor electronic diary is available from the subject, the study clinician will document the source of reactogenicity information recorded in the study database.

The signs and symptoms solicited by the diary will include systemic events of fever, feeling unusually tired or unwell, muscles aches, headache, chills, nausea, and joint pain, and local events at the SC and IV product administration site of pain/tenderness, swelling, redness, bruising, and pruritus. 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 any solicited symptoms that are ongoing after 7 days until they have resolved.

Diary data will be available in real-time to clinicians for subjects who use the electronic diary. Subjects using a paper diary will be encouraged to contact the clinic as soon as possible for any moderate or severe side effects that they experience in the 7 days post product administration. A study 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

(such as those consistent with Grade 2 or higher impairment). Additionally, other clinical concerns may prompt a study visit based on the judgment of a study clinician.

4.5.10 Follow-up through End of Study

Study follow-up will continue via clinical visits through 24 weeks after the product administration. Any subject who receives study product will be expected to continue with follow-up through the end of the study.
The visit schedule is based on intervals of time after product administration. Subjects are expected to continue follow-up according to the Schedule of Evaluations for IV or SC groups through 24 weeks, except that research sample collections will be discontinued for pregnant women or others in which it is contraindicated.
The schedule of visits, allowable windows for completing the visits, and evaluations performed at each visit are shown in the Schedule of Evaluations, Appendix I. Out of window study visits will be discouraged and recorded as protocol deviations but may be permitted at the discretion of the PI in the interest of obtaining safety and research evaluations following exposure to the investigational study product.

4.5.11 Blood Sample Collection

At intervals throughout the study, blood will be drawn for safety and immunologic assays. Blood will be drawn from the arm veins of subjects by standard phlebotomy procedures. Total blood volume drawn from each subject will not exceed the NIH CC guidelines.

4.6 Concomitant Medications

Only routine prescription medications will be entered in the database at the time of enrollment. Subsequently, the concomitant medications that will be recorded or updated in the database are those associated with an AE requiring expedited reporting, a change to pre-existing condition treatment, or the development of a new chronic condition requiring ongoing medical management. Inclusion of a concomitant medication in the database may be determined at the discretion of the PI or designee. Otherwise, concomitant medications taken throughout the study will be recorded in the subject's study chart and general medical record but will not be recorded in the database.

4.7 Criteria for Discontinuation of Protocol Participation

All subjects will be encouraged to remain on the study and continue to receive follow-up for safety. Decisions by the PI or designee to discontinue a subject from protocol participation will be made with the following criteria.

1. Subject voluntarily withdraws;
2. Pregnancy;
3. Subject develops a medical condition that is a contraindication to continuing study participation;
4. The IND Sponsor or regulatory authority stops the protocol; or
5. The IND Sponsor or PI assesses that is it not in the best interest of the subject to continue participation in the study.

For subjects who wish to discontinue protocol participation all efforts will be made to follow these subjects for safety through the last study visit. Research sample collections will be discontinued for pregnant women or others in which it is contraindicated.

4.8 CRITERIA FOR PAUSING AND RESUMING THE STUDY

4.8.1 Plan for Pausing the Study

The study team will closely monitor and review study data as they become available to make determinations regarding the presence, severity and attribution of AEs. CAP256V2LS administrations and new enrollments will be paused if any of the following criteria are met:

- **One** (or more) subject experiences a **SAE** that is assessed as related (possibly, probably or definitely) to CAP256V2LS, or

- **Two** (or more) subjects experience the same **Grade 3 or higher AE** that is assessed as related (possibly, probably or definitely) to CAP256V2LS (other than self-limited Grade 3 solicited reactogenicity or lymphocytopenia, which is an expected finding and will only trigger a pause if there are associated clinical sequelae.

4.8.2 Plan for Review of Pauses and Resuming Rules

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

The IND Sponsor MO and PI, in consultation with the PSRT, will conduct a review of available information, including the events that lead to the pause, and will make the decision to resume, amend or close the study. As part of the pause review, the reviewers may also advise on whether the study needs to be paused again for any subsequent events of the same type.

Study product administrations and new enrolments 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. Safety data reports and changes in study status will be submitted to relevant regulatory authorities in accordance with Section 5 and institutional policy.

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 subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- Solicited AEs (i.e., reactogenicity parameters as defined in Section 4.3.9) will be recorded without attribution assessments by the subject on paper or electronic diary for 7 days after product administration.
- Unsolicited AEs will be recorded in the study database with attribution assessments from product administration through the Day 28 post-product administration visit.
- SAEs (as detailed in Section 5.2) and new chronic medical conditions will be recorded as AEs through the last expected study visit or contact.

Appendix II describes how the relationship between an AE and the study product will be assessed. Also available in Appendix II is the link to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 [July 2017], which will be used to determine the severity grades of AEs in this protocol with several modifications as noted.

5.2 SERIOUS ADVERSE EVENTS

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

5.3 ADVERSE EVENT REPORTING TO IND SPONSOR

AEs that meet SAE criteria must be reported and submitted by the clinical site on an expedited basis to the IND Sponsor, VRC/NIAID/NIH, according to sponsor guidelines as follows:

- Results in death;
- Is life threatening (places the subject at immediate risk of death from the event as it occurred);
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect in the offspring of a study subject; OR
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the 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).

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

An investigator will communicate an initial SAE report within 24 hours of site awareness of occurrence to the IND Sponsor by data entry into the database, which triggers an alert to the IND Sponsor MO. Within 3 working days, a written summary by the investigator should be submitted to the IND Sponsor.

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

5.4 IND SPONSOR REPORTING TO THE FDA

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

- *Suspected Adverse Reaction* means any AE for which there is a reasonable possibility that the drug caused the AE.
- *Unexpected Adverse Event* means an AE that 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 per 21 CFR 312.32 as soon as possible but not exceeding 7 calendar days for unexpected fatal or life-threatening events, and not exceeding 15 calendar days for other qualifying events. 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

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

Reportable Event - An event that occurs during the course of human subject research that requires notification to the IRB.

For the purposes of this policy, reportable events include the following:

- Unanticipated Problems (UPs) involving risks to subjects or others
- Non-compliance (including major protocol deviations and noncompliance that is not related to a protocol deviation)
- Deaths related or possibly related to research activities
- New information that might affect the willingness of subjects to enroll or continue participation in the study

5.5.1 Unanticipated Problem

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

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **and**
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **and**
- Suggests that the research places subjects, or others (which may include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected.

A UP must be reported within 7 calendar days of an investigator becoming aware of the actual or suspected UP.

5.5.2 Non-Compliance

Non-compliance is the failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB, whether intentional or not.

Non-compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).

Non-compliance is further characterized as serious or continuing as follows:

- Serious non-compliance – Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.

- Continuing non-compliance – A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different noncompliant events.

Any actual or suspected non-compliance by any investigator or entity associated with the protocol must be reported to the IRB by the PI/designee within 7 calendar days of any investigator or individual associated with the protocol first becoming aware.

5.5.3 Protocol Deviation

A Protocol Deviation (PD) is defined as any change, divergence, or departure from the IRB-approved research protocol and are further characterized as major and minor as follows:

- Major Deviations – Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor Deviations – Deviations that do not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study.

For the reporting purposes, failure of subjects to comply with the research protocol does not represent non-compliance unless that failure is due to an action or omission of a member of the research team, for example, the failure to give adequate instruction to the subject.

A major deviation must be reported within 7 calendar days of an investigator becoming aware of an actual or suspected deviation. Although PDs are also non-compliance, these should only be reported once as deviations. Major deviations resulting in death must be reported within 24 hours of the occurrence of the event or of any member of the study team becoming aware of the death.

Researchers are responsible for monitoring their studies throughout the year for adherence to the IRB approved protocol. The purpose of this monitoring is to identify major deviations and to look for trends in minor deviations that may indicate a systemic issue in how the study is being conducted that could potentially negatively impact the rights, safety, or welfare of participants or the study's ability to produce scientifically valid results. A series of minor deviations pointing toward a more global issue that could affect the rights, safety or welfare of the participant or affect the validity of the study should be reported as a major deviation. In all other instances, a summary of minor deviations should be provided to the IRB at the time of continuing review.

5.5.4 Death

Any death of a research subject that is possibly, probably or definitely related to the research must be reported within 24 hours of an investigator becoming aware of the death.

5.5.5 New Information

New information that might affect the willingness of a subject to enroll or remain in the study should be reported within 7 calendar days of an investigator first becoming aware.

5.5.6 Suspension or Termination of Research Activities

Any suspension or termination of research activities, including holds on new enrollment, placed upon the research by the study sponsor, NIH or Institute/Center leadership, or any regulatory agency must be reported to the IRB within 7 calendar days of an investigator becoming aware.

5.5.7 Expedited Reporting to the IRB

Death related to research must be reported within **24 hours**.

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

- Actual or suspected Unanticipated Problems (UPs);
- Actual or suspected non-compliance;
- Actual or suspected Major Protocol Deviations (PDs);
- SAEs that are actual or suspected UPs;
- New information that might affect the willingness of a subject to enroll or remain in the study;
- Suspension or termination of research activities, including holds on new enrollment, placed upon the research by the study sponsor, NIH or IC leadership, or any regulatory agency.

5.5.8 Annual Reporting to the IRB

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

- Summary of UPs and non-compliance;
- AEs, including SAEs, that are not UPs, as a narrative summary statement indicating whether these events were within the expected range;
- Minor PDs (aggregate summary);
- Any trends or events which in the opinion of the investigator should be reported.

6 STATISTICAL CONSIDERATIONS

6.1 OVERVIEW

This study is a Phase 1 study in healthy adults to assess the safety, PK and protective efficacy of CAP256V2LS, an investigational human monoclonal antibody.

6.2 SAMPLE SIZE AND ACCRUAL

Trial recruitment will target about 10 healthy adults, ages 18 to 60 years, as shown in **Table 1**. The permitted accrual is 20 subjects in total to allow for additional enrollments in the event that an enrolled subject does not complete the minimum evaluations needed for PK and safety evaluations. If a subject enrolls into a study product group but does not receive a product administration or withdraws for reasons that are not safety related, then additional subjects may be enrolled to achieve the accrual target.

The primary goal of this study is to identify safety concerns associated with CAP256V2LS when administered IV or SC at the 5 mg/kg dose. Primary sample size considerations are expressed in terms of the ability to detect serious adverse experiences. The ability of the study to identify SAEs will be expressed in terms of the probability of observing a certain number of serious adverse events.

With sample size n=5 in a group, within each group there is over 90% chance to observe at least 1 SAE if the true rate is at least 0.370 and over 90% chance to observe no SAE if the true rate is no more than 0.020. With sample size n=10 in a group, within a group there is over 90% chance to observe at least 1 SAE if the true rate is no less than 0.206 and over 90% chance of observing no SAE if the true rate is no more than 0.010. Probabilities of observing 0 or 2 or more SAE within a group are presented in **Table 2** for a range of possible true event rates.

Table 2: Probability of observing 0 or at least 2 Serious Adverse Events for Different Safety Scenarios within or across Groups (n=5 or 10)

True Event Rate	n=5 Groups 1 and 2			n=10 Groups 1 and 2		
	Pr(0)	Pr(≥1)	Pr(≥2)	Pr(0)	Pr(≥1)	Pr(≥2)
0.005	0.975	0.025	0.000	0.951	0.049	0.001
0.01	0.951	0.049	0.001	0.904	0.096	0.004
0.02	0.904	0.096	0.004	0.817	0.183	0.016
0.035	0.837	0.163	0.011	0.700	0.300	0.046
0.05	0.774	0.226	0.023	0.599	0.401	0.086
0.1	0.590	0.410	0.081	0.349	0.651	0.264
0.15	0.444	0.556	0.165	0.197	0.803	0.456
0.2	0.328	0.672	0.263	0.107	0.893	0.624
0.3	0.168	0.832	0.472	0.028	0.972	0.851
0.4	0.078	0.922	0.663	0.006	0.994	0.954
0.5	0.031	0.969	0.812	0.001	0.999	0.989

Table 3 gives the upper and lower bounds for 95% exact binomial confidence intervals of the true SAE rate at possible numbers of events within a group. Within a group of size n=5, if none experience an SAE, the 95% exact confidence interval has upper bound 0.552. Within a group of size n=10, if 2 enrollees experience an SAE, the exact 95% confidence interval has lower bound 0.025 and upper bound 0.556.

Table 3: 95% Confidence Intervals for the True Rate at Possible Observed Number of Events in a Group (n=5 or n=10)

Observed Number of Events	95% Confidence Interval (n=5)		Observed Number of Events	95% Confidence Interval (n=10)	
	Lower Bound	Upper Bound		Lower Bound	Upper Bound
0/5	0.000	0.522	0/10	0.000	0.308
1/5	0.005	0.716	1/10	0.003	0.445
2/5	0.053	0.853	2/10	0.025	0.556
3/5	0.147	0.947	3/10	0.067	0.652
4/5	0.284	0.995	4/10	0.122	0.738
5/5	0.478	1.000	5/10	0.187	0.813
			6/10	0.262	0.878
			7/10	0.348	0.933
			8/10	0.444	0.975
			9/10	0.555	0.997
			10/10	0.692	1.000

6.3 STATISTICAL ANALYSIS

Enrollment of CAP256V2LS recipients may occur on the same day as product administration at Visit 02 (Day 0) or in advance of product administration at Visit 01R (Day -42 to Day 0). All subjects who receive product administration will provide safety data.

The primary analysis cohort will include all enrolled subjects who receive product administration and will be analyzed according to the assigned group.

All statistical analyses will be performed using SAS and R statistical software.

6.3.1 Analysis Variables

The analysis variables consist of baseline, safety parameters and PK. Descriptive statistics will be used to summarize baseline characteristics, inclusive of demographics and safety laboratory measurements.

6.3.2 Safety Analysis

Safety evaluation will be performed over the primary analysis cohort. The number and percentage of subjects with one or more AEs will be summarized by dose group along with the exact 95% confidence intervals of the AE rate. For subjects experiencing more than one AE, they will be counted once under the event of highest severity. In addition, a complete listing of AEs for each subject will provide details such as severity, duration, and relationship to study product. Summaries will be provided for any solicited or unsolicited AEs.

6.3.2.1 Solicited Reactogenicity

Solicited AE data will be collected after product administration. The number and percentage of subjects experiencing each type of solicited sign or symptom will be tabulated by severity and by route group (i.e. IV dose group and SC dose group) and overall. Subjects with multiple occurrences of the same event will be counted once using the event of highest severity.

6.3.2.2 Adverse Events

All reportable AEs will be recorded and coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The number and percentages of subjects with each unsolicited AE will be tabulated by severity and relationship to the study product, and by dose group and overall (i.e., pooled IV dose groups and pooled SC and IV dose groups). Subjects with multiple occurrences of the same event will be counted once using the event highest severity or strongest relationship to the study treatment.

A by-subject listing of all unsolicited AEs will provide details including severity, relationship to treatment type, seriousness, new medical condition status, onset and end date, duration, and outcome.

6.3.2.3 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.

6.3.3 Pharmacokinetics Analysis

PK analysis will be performed over the PP cohort. Blood samples for PK evaluations will be collected at defined time-points as listed in Appendix I.

Individual Subject Pharmacokinetic Analysis: A non-compartmental (NC) PK analysis will be performed using Phoenix 7.0 (Certara^{R}), PKPlus or a similar program on the CAP256V2LS concentration data generated from each subject. Individual subject and route group concentration vs time profiles will be constructed in linear and semi-log scales. In the NC analysis the maximum concentration (Cmax) and time of maximal concentration (Tmax) will be taken directly from the observed data. The area under the concentrations vs. time curve (AUC) will be calculated using the trapezoidal method and determined out to the final concentration collected. If a subjects CAP256V2LS concentration falls below the quantitative limit (QL) of the assay before the final of PK sample collection, the sample with concentration below the QL will be assigned a CAP256V2LS concentration value of "0" for AUC calculations.

Population Pharmacokinetic Analyses: Population PK analyses will be performed on the PK data following IV and SC administration to determine compartmental PK parameters with the PK program NONMEM 7.3 or later (ICON^{R}). Based on preclinical PK results for CAP256V2LS and known PK behavior studies of mAbs, two-compartment model will be used (subroutine ADVAN4 TRANS4). Both zero order and first order absorption following SC administration will be evaluated and a lag time included if a delay is seen in the raw data figures. The First Order Conditional Estimation Method with Interaction (FOCEI) will be used. The population analysis will generate estimates for clearance (CL) central and peripheral volumes of distribution (Vd_1 and Vd_2), inter-compartmental clearance (Q), CL and SC bioavailability (F). Total volume of distribution at steady-state (Vdss), will be calculated as the sum of $Vd_1 + Vd_2$. Alpha and beta half-lives will be calculated from CL, Q, Vd_1 and Vd_2 using standard equations (M. Gilbaldi and D Perrier, Pharmacokinetics Marcel Dekker,1975). While the number of subjects is expected to be sufficient to characterize the typical PK parameters and their between-subject variabilities (BSVs), the sample number is too small for a robust broad population PK covariate analysis.

6.3.4 Interim Analysis

Analysis of safety and PK data will occur at the completion of the study and may be done at interim time points at the discretion of the PI.

7 PHARMACY PROCEDURES

The study groups are shown in Table 1.

7.1 STUDY PRODUCT

This study includes one investigational monoclonal antibody product as follows:

- VRC HIVMAB0102-00-AB (CAP256V2LS) is a sterile aqueous buffered solution filled into 10 mL single-dose vials. Each vial contains 6.25 ± 0.1 mL at a concentration of 100 ± 10 mg/mL in formulation buffer. The formulation buffer is composed of 20 mM Sodium Phosphate, 100 mM Sodium Chloride, 75 mM L-Arginine HCl, 3% (w/w) Sucrose, and 0.01% (w/v) Polysorbate 80 at pH 7.0.

7.2 STUDY PRODUCT HANDLING INFORMATION

CAP256V2LS and R-Gene 10 (added as a stabilizing agent to IV doses) are not hazardous chemicals under U.S. OSHA Hazard Communication (29 CFR 1910.1200) and the Department of Transportation (49 CRF 172.101) standards.

Handling of the study product should follow general laboratory safety practices to prevent unintended exposure. Protective gloves, mask, and safety glasses should be worn, and exposed skin should be covered with sleeve protectors and/or a lab coat.

In the event of a spill, procedures include physical containment with common absorbent materials, cleaning by wiping the contaminated area with a mixture of one-part bleach mixed with nine parts water (10% bleach solution) and disposal in appropriate containers. Spills on skin or splashes in eyes should be flushed with running water for at least 15 minutes. In case of ingestion, wash mouth with water and seek medical attention. Waste materials should be disposed of in accordance with standard institutional procedures.

For administration of the prepared product in the clinical setting, the clinical staff should practice universal precautions and dispose of the used needles, syringes and IV bags in keeping with the required practices for handling sharps in the medical facility.

7.3 STUDY PRODUCT THAWING INSTRUCTIONS

CAP256V2LS is a clear, colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. CAP256V2LS is a highly concentrated protein solution and may develop opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at 15°C to 27°C or storage at 2°C to 8°C.

The following instructions apply to thawing CAP256V2LS:

1. Thaw vial(s) for a minimum of 90 minutes at 15°C to 27°C after removing from the freezer. Vials must not be moved directly from the freezer to storage at 2°C to 8°C.
2. Following initial thaw, keep the material at 15°C to 27°C during the entire preparation period until use, up to the maximum storage times described in Section 7.5.3.
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.

a. Visually inspect the vials; if 10 or fewer visible particles are present, the vial may be used for product preparation.
b. If more than 10 particles are observed, return the vials to 2°C to 8°C storage. If the particles re-dissolve or if 10 or fewer visible particles are present within the maximum storage times described in Section 7.5.3, the vials may be used for product preparation.

If freshly thawed material is not administered within 24 hours of thaw, follow the storage information provided in Section 7.5.3.

Thawed and refrigerated vialed product must be equilibrated at 15°C to 27°C for a minimum of 60 minutes before preparation and must be used for dose preparation within 8 hours. If not used within this time period, it may be returned to 2°C to 8ºC, within the storage time limits provided in Section 7.5.3.

7.4 STORAGE AND TEMPERATURE EXCURSIONS

Study product vials must be stored until use at the temperature specified on the label, -35°C to -15°C, in a qualified, continuously-monitored, temperature-controlled freezer. Each vial is intended strictly for single use; refreeze and reuse after thaw should be avoided.

In the case of storage or shipping/handling temperature excursions outside of the normal allowance for the storage device, the following procedure is to be followed:

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

7.5 LABELING OF CAP256V2LS INVESTIGATIONAL PRODUCT

Vials of CAP256V2LS will be individually labeled with the name of the material, volume, lot number, concentration, storage instructions, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

7.6 PREPARATION OF STUDY PRODUCT ADMINISTRATION

CAP256V2LS should be prepared using aseptic technique in a biosafety cabinet. Only the required vials should be present in the preparation unit during the preparation process, and medication labels should be strictly segregated to avoid mix ups.

7.6.1 Preparation for IV Administration

For each IV infusion order, the subject's weight, dose level, and study group will be included in the pharmacy order. To prepare an IV infusion, the pharmacist will: 1) calculate the total milligrams of CAP256V2LS needed, 2) retrieve the minimum number of thawed vials required to prepare the full dose and the 0.9% Sodium Chloride Injection USP, 100 mL partial fill in 150 mL IV bag (no latex, PVC or DEHP, equivalent but not limited to B.Braun NDC: 00264-1800-32). After vials are thawed, prior to preparation for administration in the IV bag, vials should be gently swirled for 30 seconds while avoiding foaming. DO NOT SHAKE THE VIAL. Follow the following preparation instructions:

1. Remove 25mL of saline from the 100 mL normal saline IV Bag.
2. Add 20 mL of 10% Arginine HCL (R-Gene 10, Pfizer), and invert gently to mix
3. Add the necessary volume of CAP256V2LS to 95 mL saline + Arginine HCl
4. Remove all air from the IV bag

An in-line filter infusion set is required for IV product administrations and must comply with the following specifications: 1.2-micron PES (polyethersulfone) filter membrane, DEHP-free, latex-free (equivalent but not limited to Braun #473994 filter extension set). After the in-line filter is added to the tubing, the administration set must be primed. At the end of product administration, the IV administration set must be flushed with about 25 mL (or appropriate volume) of normal saline.

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

7.6.2 Preparation for SC Administration

For each SC administration order, the subject's weight, dose level, and study group 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 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.

The needed volume of CAP256V2LS must be withdrawn from the vial into 1 to 4 syringes using a 5-micron filter needle. A new filter needle must be used for each syringe. The filter needle must be discarded prior to dispensing and replaced with a needle suitable for SC injection at the time of administration. The product may be administered by direct SC injection with needle and syringe. 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.

7.6.3 Handling of Prepared Product for IV or SC Administration

After product preparation in an IV bag, the prepared CAP256V2LS may be stored at 15°C to 27°C for a maximum of 4 hours total including the infusion time. Prepared IV bags may NOT be stored at 2°C to 8°C. Product may not be stored in direct sunlight.

After preparation in syringes for SC administration, the prepared CAP256V2LS may be stored at 2°C to 8°C up to 24 hours or at controlled room temperature (15°C - 27°C) up to 4 hours. Product may not be stored in direct sunlight.

If compounded SC preparations have been stored at 2°C to 8°C, equilibrate for approximately 30 min at room temperature before use.

7.7 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 agent supplies. Electronic documentation as well as paper copies may be used.

7.8 STUDY PRODUCT DISPOSITION

The empty vials and the unused portion of a vial will be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with the institutional or pharmacy policy. Partially used vials will not be administered to other subjects or used for in vitro experimental studies.

Any unopened vials that remain at the end of the study will be returned to the VRC or discarded at the discretion of the sponsor in accordance with policies that apply to investigational agents. Vials will be disposed of in accordance with institutional or pharmacy policy.

8 HUMAN SUBJECT PROTECTIONS AND ETHICAL OBLIGATIONS

This research will be conducted in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements.

8.1 INSTITUTIONAL REVIEW BOARD

The protocol, proposed informed consent form, other written subject information, and any proposed advertising material will be submitted to the IRB for review and written approval. 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 adverse events as described in Section 5.5.

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

8.2 INFORMED CONSENT

The study informed consent form (ICF) is provided as a separate document and describes the investigational product to be used and all aspects involved in protocol participation.

The PI or designee is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated risks and benefits of the study and before any protocol-specific procedures or study product is administered. The AoU will be completed before the study ICF is signed.

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

8.3 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the investigators, the Investigational New Drug (IND) and regulatory authorities as appropriate. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB and/or FDA.

8.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by The Emmes Company, LLC, the Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by Emmes research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

8.5 RISK/BENEFIT ASSESSMENT

8.5.1 Potential Risks

Risk of CAP256V2LS: Transient declines in lymphocyte counts, up to grade 4, without associated clinical sequelae, were observed in 8 HIV negative participants in the CAPRISA 012B study. The DSMB concluded that this transient laboratory abnormality did not represent a safety concern given its transient nature and the absence of associated clinical findings.

Risks of mAb Administration: Administration of mAbs may cause immune reactions such as acute anaphylaxis, cytokine release syndrome, serum sickness and the generation of anti-drug antibodies. However, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of mouse mAbs that would have a risk of human anti-mouse antibodies[33]. In this regard, as CAP256V2LS is expected to have a low risk of such side effects since it is directed against a viral antigen and is human in origin.

Typically, the side effects of mAbs are mild to moderate and may include local reactions at the injection site (including pain, redness, bruising, swelling) and systemic reactions such as fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain. When infused intravenously, infusion-related events commonly occur within the first 24 hours after initiation of mAb administration. Infusion related reactions are common with licensed therapeutic mAbs, and typical symptoms include mild fevers, rigors, backpain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, or changes in heart rate and blood pressure[20]. Infusion related reactions are managed by temporarily stopping the infusion, administering histamine blockers and restarting the infusion at a slower rate[34]. Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections[33]; 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 cell surface targets on lymphocytes shows that infusion of a mAb may be associated with cytokine release, causing a reaction known as cytokine release syndrome (CRS)[35]. In contrast to the milder infusion reactions described above, CRS is rare and mechanistically associated with indiscriminate activation of immune cells leading to a cytokine storm characterized by severe headaches, low back pain, nausea, vomiting, diarrhea, fever, disseminated intravascular coagulation and other symptoms of critical illness including respiratory and renal failure requiring intensive care treatment.

Delayed allergic reactions that include a serum sickness type of reaction characterized by urticaria, fever, lymph node enlargement, and joint pains, typically occur several days after mAb exposure and are more commonly associated with chimeric types of mAbs[33].

Risks of IV administration of R-Gene 10: R-Gene 10, Pfizer (10% arginine-HCL) is FDA approved as an intravenous stimulant for diagnostic testing. The recommended adult dose of R-Gene 10 for the U.S. FDA approved indication is 30g, which is 15 times higher than the 2g that is to be used in the clinical study. Side effects reported at doses 15 times higher than those proposed to be used in this study are generally related to excessive infusion rates and include nausea, vomiting, headache, flushing, numbness and local venous irritation. Other more severe reactions such as hypersensitivity reactions including anaphylaxis, hematuria, and extravasations resulting in burns and skin necrosis have rarely occurred [36]

Risks of IV infusions or SC injections: General risks of methods that use a needle include stinging, discomfort, pain, soreness, redness, bruising, swelling or a tiny cut at the needle insertion site.

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

this study, an IV line that can be used for blood collection may be placed in the arm and left in place for several hours on days when there is product administration for frequent PK blood draws. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site and rarely, infection, vein irritation (phlebitis), or blood clot.

Risks of Study mAb on the fetus or nursing infant: We do not know the possible effects of the study product on the fetus or nursing infant. Women of reproductive potential will be required to agree to use an effective method of birth control beginning 21 days prior to enrollment and continuing through the end of study.

Because this is a research study, women of reproductive potential will be tested for pregnancy prior to administration of study product and asked to notify the site immediately upon learning of a pregnancy during this study. In the case of pregnancy, subjects will continue to be followed for safety. Research sample collections will be discontinued for pregnant women. The subject will be contacted to ask about the outcome of the pregnancy that begins during the study.

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

Risks of Screening Procedures: The risks of screening procedures can be found in the VRC's screening protocol, VRC 500 (NIH 11-I-0164, NCT01375530) used for all VRC IND studies conducted at the NIH Clinical Center.

8.5.2 Assessment of Potential Risks and Benefits

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

The plan for reduction of known and unknown risks to participants includes appropriate training of study personnel; education of study subjects for participation in care throughout the study; monitoring of study participants' health status and experiences; withdrawal from study procedures upon evidence of difficulty, contraindication, or a significant adverse event; and referral for treatment, counseling or other necessary follow-up. The VRC Clinical Trials Program Risk Management Plan guides the reduction and mitigation strategies applied to the known and unknown risks associated with study participation and to study operations. As study subjects will not receive direct health benefit from study participation or product administration, no alternative procedures are planned. The alternative course of action is to choose not to participate.

8.6 PLAN FOR USE AND STORAGE OF BIOLOGICAL SAMPLES

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

8.6.1 Use of Samples, Specimens and Data

Samples, specimens and data collected under this protocol may be used to conduct protocol-related safety, and immunogenicity evaluations, exploratory laboratory evaluations related to HIV, exploratory laboratory evaluations related to mAb, vaccine or infectious disease research in general and for research assay validation.

Genetic testing may be performed in accordance with the genetic testing information that was included in the study ICF. Genetic testing, including allotyping may be done on collected specimens in an effort to evaluate for allotype-specific effects on pharmacokinetics.

8.6.2 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 VRC Vaccine Immunology Program 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).

8.6.3 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 with non-NIH investigators and any clinical information shared about those samples would similarly require prior IRB approval. The research use of stored, unlinked or unidentified samples will be exempt from the need for prospective IRB review and approval according to NIH IRB policy.

At the time of protocol termination, samples will remain at the VRC Vaccine Immunology Program facility or VRC laboratories or, after IRB approval, will be 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.

8.6.4 Loss or Destruction of Samples, Specimens or Data

Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) will be reported to the IRB. The Protocol Chair or PI will also notify the IRB if the decision is made to destroy the remaining samples.

8.7 SAFETY OVERSIGHT

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 CTP designated Safety Officer (SO) conducts a daily safety review of clinical data per VRC CTP Standard Operating Procedures.

The Protocol Safety Review Team (PSRT) will be comprised of the Principal Investigator (PI), Associate Investigators, Study Coordinator, Protocol Specialists, other study clinicians, and the IND Medical Officer (MO). The PSRT 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 then on a monthly basis through completion of the last study visit. The PSRT will evaluate and respond to safety concerns in a timely manner.

8.8 CONFLICT OF INTEREST POLICY

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

9 ADMINISTRATIVE AND OPERATIONAL OBLIGATIONS

9.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Protocol amendments must be made only with prior approval of the IND Sponsor and with agreement from the PI and MO. All study amendments will be submitted to the IRB for approval.
The IND Sponsor, the IRB, OHRP, the PI, Protocol Chairs, and/or the 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, 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 IND Sponsor (VRC/NIAID/NIH), IRB, NIH, 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.

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

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a designated CRO. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

9.4 DATA COLLECTION AND SHARING

9.4.1 Data Collection

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

9.4.2 Source Documents

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 (R2) GCP, applicable regulations, 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.

9.4.3 Data Sharing

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

9.5 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. The VEC Quality Management Plan will be used to perform quality management for this trial.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

The monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

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

9.6 LANGUAGE

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

9.7 RESEARCH-RELATED INJURIES

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

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APPENDIX I: SCHEDULE OF EVALUATIONS

Schedule of Evaluations: Group 1 (5 mg/kg IV)																			
Visit Number			01R	02	02A	02B	02C	02D	03	04	06	07	08	09	10	11	12	13	14
Time After Infusion				Pre	EOI	1hr	3h	4h	24hr	48hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study			-42 to -0	D0	D0	D0	D0	D0	D1	D2	D7	D14	D21	D28	D56	D84	D112	D140	D168
Clinical	Tube^	Screen	Enroll	Day of infusion															
VRC 500 Screening Consent		X																	
VRC 611 Informed Consent, AoU			X																
[2]Physical examination		X	X	X	X				X	X	X	X	X	X	X	X	X	X	X
Complete Med History at screen; then interim med history		X	X	X					X	X	X	X	X	X	X	X	X	X	X
[3]CAP256V2LS Administration				X															
Begin 7-day Diary Card				X															
CBC / differential	EDTA	3		3					3		3	3		3		3			
[4]ALT, creatinine	GLT	4		4					4		4	4		4		4			
[4]CMP	GLT	X		X								X							
[5]Pregnancy test: urine or serum		X	X	X								X					X		X
[5]Pregnancy prevention counseling		X	X	X								X					X		X
HIV Ag/Ab Combo	EDTA	3									3								
HIV risk-reduction counseling		X		X							X								
Research Samples																			
PK	SST			4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Serum	SST	16	16	16[6]						16	16	16	16	16[6]	16	16	16	16	16[6]
PBMC	EDTA	20							20										20
Daily Volume (mL)		**46**	**16**	**27**	**4**	**4**	**4**	**4**	**31**	**20**	**30**	**27**	**20**	**27**	**20**	**27**	**20**	**20**	**40**
Cumulative Volume (mL)		**46**	**62**	**89**	**93**	**97**	**101**	**105**	**136**	**156**	**186**	**213**	**233**	**260**	**280**	**307**	**327**	**347**	**387**

Visit windows: Schedule all visits with respect to Day 0. Visit 02A (+10 min); Visits 02B and 02C (±10 min); Visit 02D (+2 hrs); Visits 03, 04 (± 6 hrs); Visits 06, 07, 08, 09 (±2 days), and Visits 10, 11, 12, 13 and 14 (±7 days).

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

[2] Screening includes physical exam with vital signs (blood pressure, temperature, pulse respiratory rate), height and weight. Research blood samples will be collected anytime during screening through enrollment and will not be subject to the "84-days prior to enrollment" restriction. At other visits, if medically indicated, perform a targeted exam. Otherwise only vital signs are required, except at Visit 02 when the current weight is also obtained to use for ordering the study product, dosed based on "mg/kg."

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

[4] ALT, and creatinine will be collected at all scheduled timepoints. Comprehensive metabolic panel (CMP) will be collected at screening, baseline, and 2 weeks after product administration and as needed at additional timepoints. CMP includes sodium, potassium, chloride, total CO2, creatinine, glucose, urea nitrogen, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, calcium, total protein. Grade 1 laboratory abnormalities in asymptomatic subjects are not reportable.

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

[6] ADA assessed from serum samples at timepoints indicated and at additional clinically relevant timepoints per PI discretion.

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

Schedule of Evaluations: Group 2 (5 mg/kg SC)																	
Visit Number			01R	02	02A	03	04	05	06	07	08	09	10	11	12	13	14
Time After Infusion				Pre	EOI	24hr	48hr	72hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1] Day of Study			-42 to 0	D0	D0	D1	D2	D3	D7	D14	D21	D28	D56	D84	D112	D140	D168
Clinical	Tube^	Screen	Enroll	Day of injection													
VRC 500 Screening Consent		X															
VRC 611 Informed Consent, AoU			X														
[2] Physical examination		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] CAP256V2LS Administration				X													
Begin 7-day Diary Card				X													
CBC / differential	EDTA	3		3		3			3	3		3		3			
[4] ALT, creatinine	GLT	4		4		4			4	4		4		4			
[4] CMP	GLT	X		X						X							
[5] Pregnancy test: urine or serum		X	X	X						X					X		X
[5] Pregnancy Prevention counseling		X	X	X						X					X		X
HIV Ag/Ab Combo	EDTA	3							3								
HIV risk-reduction counseling		X		X					X								
Research Samples																	
PK	SST			4		4	4	4	4	4	4	4	4	4	4	4	4
Serum	SST	16	16	16[6]			16	16	16	16	16	16[6]	16	16	16	16	16[6]
PBMC	EDTA	20				20											20
Daily Volume (mL)		**46**	**16**	**27**	**0**	**31**	**20**	**20**	**26**	**27**	**20**	**27**	**20**	**27**	**20**	**20**	**40**
Cumulative Volume (mL)		**46**	**62**	**89**	**89**	**120**	**140**	**160**	**186**	**213**	**233**	**260**	**280**	**307**	**327**	**347**	**387**

Visit windows: Schedule all visits with respect to Day 0. Visit 02A (+10 min); Visits 03, 04, 05 (± 6 hrs); Visits 06, 07, 08, 09 (±2 days); Visits 10, 11, 12, 13, 14 (±7 days

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

[2] Screening includes physical exam with vital signs, (blood pressure, temperature, pulse, respiratory rate), height and weight. At other visits, if medically indicated, a targeted exam is performed. Research blood samples will be collected anytime during screening through enrollment and will not be subject to the "84 days prior to enrollment" restriction. Otherwise only vital signs are required, except at Visit 02 when the current weight is also obtained to use for ordering the study product, dosed based on "mg/kg."

[3] The PK blood draw "visits," defined by hours after an injection, are relative to the exact time of the end of injection (EOI). All subjects will be observed for at least 2 hours after product administration.

[4] ALT, and creatinine will be collected at all scheduled timepoints. Comprehensive metabolic panel (CMP) will be collected at screening, baseline, and 2 weeks after product administration and as needed at additional timepoints. CMP includes sodium, potassium, chloride, total CO2, creatinine, glucose, urea nitrogen, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, calcium, total protein. Grade 1 laboratory abnormalities in asymptomatic subjects are not reportable.

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

[6] ADA assessed from serum samples at timepoints indicated and at additional clinically relevant timepoints per PI discretion

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

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APPENDIX II: ASSESSMENT OF AE RELATIONSHIP TO STUDY PRODUCT AND

ADVERSE EVENT SEVERITY GRADING

Assessment of Relationship of an Adverse Event to Study Product

The relationship between an AE and the study product will be assessed by the investigator on the basis of clinical judgment and the definitions below.

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

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

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

Grading the Severity of an Adverse Event

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 [July 2017] will be used to determine the severity grades of AEs in this protocol and is 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

Several modifications were made to the table as follows:

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

PRINCIPAL INVESTIGATOR: Richard Wu, MD

STUDY TITLE: VRC 611 (20I0096): A Phase I Safety and Pharmacokinetic Study to Evaluate a Human Monoclonal Antibody (mAb) VRC-HIVMAB0102-00-AB (CAP256V2LS) Administered via Subcutaneous and Intravenous Injection in Healthy Adults

STUDY SITE: NIH Clinical Center

Cohort: Healthy Volunteer

Consent Version: October 07, 2022, Version 3.0

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Richard Wu, M.D., [redacted]

Study Coordinator: [redacted]

KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

This is a study of an experimental drug called CAP256V2LS. CAP256V2LS is a monoclonal antibody (mAb) that targets HIV. CAP256V2LS is currently being evaluated separately in the South African CAPRISA 012B study. The main purpose of this study is to further evaluate if CAP256V2LS is safe and how your body responds to it. We also want to check if your body will recognize CAP256V2LS and make an immune response to it. You cannot get HIV from CAP256V2LS.

About 10 to 20 people will take part in this study at the NIH Clinical Center in Bethesda, MD. If you decide to take part, you will be in the study for about 24 weeks (6 months) and get CAP256V2LS one time in one of two ways: given into a vein in your arm, intravenously (IV), or as an injection in the fat under your skin, subcutaneously (SC). This information will be helpful for future uses of the product. This will also allow us to see how much of the antibody stays in the body after only one dose. If you get CAP256V2LS in the vein, it will be mixed with an FDA approved product called R-Gene® 10, that contains L-arginine, a naturally occurring amino acid.. R-Gene 10 is added to CAP256V2LS in the IV bag to keep it stable. R-Gene 10 has been used in people before at a dose 15 times higher than the dose you will get in this study

If you have side effects from CAP256V2LS, we expect them to be like the side effects that occur with similar mAbs. These side effects usually occur within the first 24 hours after the mAb is given and include local symptoms such as pain, redness, swelling, and itching. Also,

fever, tiredness, body aches, headache, chills, nausea, and joint pain may occur. The following side effects, although rare, may occur including trouble breathing, itchiness, rash, hives, swelling, or chest pain. Some mAbs have a risk of serious allergic reactions that can be life threatening.

During the study, we will collect blood samples from you. Some of your blood will be stored for future research. You will be compensated for your time and inconvenience for taking part in this study. You will not benefit from this study.

To be in this study, you must be willing to use an effective birth control method and not become pregnant from at least 21 days prior to enrollment through the end of the study, if you are a woman who is able to get pregnant.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

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 or prevent HIV infection. Using antibodies is one way to prevent HIV infection that seems promising. Antibodies are naturally made by the body to fight germs so that people remain healthy. This study will test an antibody called CAP256V2LS. CAP256V2LS has been used in the lab to block an HIV-like virus from causing infection in animals. Monoclonal means that all the antibodies in CAP256V2LS are the same. The U.S. Food and Drug Administration (FDA) only allows it to be used for research because it is an experimental product.

"Experimental" means that the study mAb has not been approved by the Food and Drug Administration (FDA). The FDA allows this mAb to be used for research purposes only. R-Gene 10 is approved by the FDA and will be used for research purposes in this study. We do not know if CAP256V2LS will protect you from HIV.

You cannot get HIV from CAP256V2LS.

The purpose of this research study is to see if CAP256V2LS is safe and how your body responds to it. We will tell you if we learn anything new during this study that might cause you to change your mind about staying in the study. At the end of the study, we will tell you when study results may be available and how to learn about them.

WHAT WILL HAPPEN DURING THE STUDY?

The study will have two groups as shown in the study plan table. Each group will have 5 to 10 people in it. If you agree to take part in this study, you will only get one dose of CAP256LSV2LS. You will get CAP256V2LS in one of two ways; given into a vein in your arm, intravenously (IV), or as an injection in the fat under your skin, subcutaneously (SC). This information will be helpful for future uses of the product. We will tell you which group you are in. Your body weight is used to calculate the amount of CAP256V2LS you will get. You will be weighed on the day CAP256V2LS is to be given.

You will be in the clinic for about 8 hours on the day that CAP256V2LS is given. This will allow us to see if the dose of the antibody is safe and how long it lasts in the body. Other clinic visits will take 30 minutes to 2 hours. Any participant who is assessed as being unwell or has ongoing symptoms will be asked to remain in the clinic until evaluation and discharge by a study clinician. This includes the possibility of an overnight inpatient stay to evaluate for safety. In keeping with the NIH CC policy and good medical practice, acute medical care will be provided to participants for any immediate allergic reactions or other injury resulting from participation in this research study.

The table below shows the study plan:

Groups	**Study Products**	**Participants per Group**	**Dose (mg/kg) and Route Administered**	**Day 0**
1	CAP256V2LS	5 (up to 10)	5 mg/kg IV	X
2	CAP256V2LS	5 (up to 10)	5 mg/kg SC	X
Total Participants		10 (up to 20, if needed)		

If you are a woman who can get pregnant, we will do a pregnancy test before you get CAP256V2LS. The results of the test must be negative in order to get CAP256V2LS.

Group 1

If you are assigned to Group 1, an IV line (thin tube) will be placed in a vein in your arm on the day you get the study product. CAP256V2LS will be mixed with R-Gene 10 in the IV bag before it is given to you. R-Gene10 helps CAP256V2LS stay stable when given in an IV. Only people assigned to Group 1 will get R-Gene10. The CAP256V2LS with R-Gene 10 will be given directly into your vein using a pump to control how fast it goes in. The goal is to give the CAP256V2LS mixed with R-Gene 10 in about 30 minutes, but it may take longer. If you have side effects, the rate may be slowed down or stopped. At the end of your infusion, we will monitor you for any side effects for at least 2 hours.

We will also place an IV line in your other arm for blood collection during the visit to avoid sticking you with a needle multiple times. We will draw your blood before and right after the infusion, and then 3 more times during the 4-6 hours after the infusion. You will be allowed to go home about 4-6 hours after the infusion, as long as you do not have concerning side effects. If you have side effects, we will treat them. You will also be asked to come back to the clinic at least 2

times during that first week after the infusion and for about 9 more follow-up visits over the next 6 months for safety evaluation and blood sample collection. We will collect about 1 to 6 tubes of blood from you at each study visit (this is less than one half of a cup or 4 tablespoons). The total amount of blood drawn from you during the entire study visit will not exceed the NIH Clinical Center guidelines.

Group 2

If you are assigned to Group 2, we will use a small needle to inject CAP256V2LS into the fatty tissue of your belly. We may use your arm or thigh instead. Depending on your weight, you will receive between 1 to 4 injections. You will be monitored for at least 2 hours after getting your injection(s). If there are no safety concerns, you will be allowed to leave the clinic. We will collect blood samples from you before the injection. You will also be asked to come back to the clinic at least 3 times during that first week after the infusion and for about 9 more follow-up visits over the next 6 months for safety evaluation and blood sample collection. We will collect about 2 to 6 tubes of blood from you at each visit (this is less than one half of a cup or 4 tablespoons). The total amount of blood drawn from you during the entire study will not exceed the NIH Clinical Center guidelines.

Follow-Up after CAP256V2LS Administration

We will give you a measuring tool and thermometer and ask you to check your temperature every day for 7 days after you get CAP256V2LS. You will need to record your highest temperature and any symptoms you have. You will use the measuring tool to measure any redness, swelling, or bruising you may have at the injection site. You will get a password to a secure website to record this information. If you do not have internet access, you may use a paper diary instead.

You should tell a VRC nurse or doctor as soon as possible if you have any moderate to severe side effects after you get CAP256V2LS. You can reach the staff by phone 24 hours a day, seven days a week. You may need 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 will last 30 minutes to 2 hours and allow us to check you for any health changes or problems. We will ask you how you are feeling and if you have taken any medications. We will draw about 1-6 tubes of blood at scheduled study visits. We will tell you right away if any ofyour test results show a health problem.

We will use some blood samples to study if your body develops an immune response to CAP256V2LS. These tests are for research purposes only and are not for checking 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 answer the research questions. The visit schedule is a little flexible, but it is important that you follow the schedule as closely as possible. You should try to not miss any visits. You should contact the clinic staff as soon as possible if you need to change the date or time of any study visit.

HIV TESTING AND COUNSELING

HIV risk-reduction counseling and testing will be provided to you if you take part in this study. We will test you for HIV. We will tell you how to remain HIV-uninfected and give you prevention resources. If you are infected with HIV, you will not be able to receive CAP256V2LS.

We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners that may be at risk because of your HIV infection.

If you have questions 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

This study will be monitored by a group of physicians and scientists at NIH. This group will review the study information and will pay close attention to any reactions.

GENETIC TESTING

Some of the blood drawn from you during this study will be used for genetic tests. In research, some genetic tests are done to see if genetic differences in people cause different types of immune responses. Some of the genetic tests will be done in a research laboratory from your stored samples. The performance of these tests in the research laboratory is not for health care purposes.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

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for about 24 weeks (6 months). There are 13 planned clinic visits for the IV group and 14 planned clinic visits for the SC group. You will be in the clinic for about 8 hours on the day that CAP256V2LS is given. Other clinic visits will take 30 minutes to 2 hours. You will be seen in clinic 3-4 times the week you get CAP256V2LS, then you will be seen weekly for 1 month, and then monthly until the end of the study 24 weeks later.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to enroll between 10 to 20 people.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

Possible Risks of CAP256V2LS

CAP256V2LS is currently being evaluated separately in the South African trial CAPRISA 012B, which started enrollment on July 13, 2020. As of August 23, 2021, 42 HIV-negative participants have been enrolled into the CAPRISA 012B study. The safety data described below is taken from the CAPRISA 012B study, from currently ongoing VRC 611 study, and from studies with other antibodies that are like CAP256V2LS that may work the same. Most side effects tend to happen within the first 24 hours.

While most participants reported some side effects, most side effects were not dangerous and cleared up quickly. A low white blood cell count (also known as lymphocytopenia) was a common

event seen in study participants in South Africa. White blood cells help the body fight infection and disease. In the CAPRISA 012B study, low white blood cell counts were seen within a day after participants got CAP256V2LS, and the cell counts quickly improved with no symptoms or other known problems. Similar decreased white blood counts were seen in 8 (80%) of participants in VRC 611. All of these events were detected in laboratory tests, were not associated with any symptoms, and resolved within a week without any residual effects.

Side effects to CAP256V2LS-like antibodies given by IV dosing may include fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart, or chest pain. These symptoms usually go away within a few minutes to hours after the product is given. We are giving CAP256V2LS at a controlled rate. If you develop symptoms while CAP256V2LS is being given, tell the nurse right away. Slowing or stopping the flow rate may help improve the symptoms.

Side effects to CAP256V2LS-like antibodies given by SC dosing may include mild itchiness, redness and/or swelling at the site of injection. Tiredness, muscle pain outside the injection site, and headache have also been reported. These symptoms usually clear within 1 to 2 days.

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

Anaphylaxis is one type of allergic reaction that may happen soon after an antibody product is given. This reaction can include difficulty breathing, low blood pressure, hives, rash, or swelling in the mouth and face.

Serum sickness is a type of reaction that may happen several days or weeks after an antibody 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. CAP256V2LS is not expected to increase the risk of serious infections because it attacks a virus and does not target the human immune system.

Possible Risks of R-Gene 10

Side effects to R-Gene 10 have happened at doses 15 times higher than the amount that will be used in this study. These side effects are generally related to excessive infusion rates and can include nausea, vomiting, headache, flushing, numbness and local venous irritation. Other more severe reactions have rarely occurred such as hypersensitivity reactions including anaphylaxis, blood in urine, and leaking of fluid into surrounding tissue resulting in burns and skin necrosis.

Unknown Risks

CAP256V2LS may have other side effects even serious or life-threatening ones that we do not yet know about. Taking part 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. Please tell the study staff about any side effect you think you are having. This is important for your safety.

Possible Risks of Injections (IV or SC)

Temporary stinging, pain, redness, soreness, itchiness, swelling, discomfort or bruising.

Possible 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. Problems at the IV site are usually mild. Rarely, there may be an infection, vein irritation, nerve problem, or blood clot.

Possible Risks of Genetic Testing

Unplanned release of information that could be used by insurers or employers to discriminate against you or your family; discovering a gene that suggests risk of disease for you or your family.

The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

Possible Risks from Stored Samples

We will collect blood samples from you during the study. We will keep these samples for future research indefinitely to learn more about mAbs and 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.

There is a small chance that information from your medical records could be given to someone who should not get it without your permission. It is possible for someone to use that information to discriminate against you when you apply for insurance or employment. Similar problems may occur if you give information about yourself or agree to have your medical records released.

Labeling of Stored Samples

Your stored samples will be labeled by a special code or number and not your personal information. Only the study team can link this code to you. Any identifying information about you (like name or date of birth) will be kept as confidential as allowable by law.

Possible Risks of Data Sharing

Information in the shared databases could be linked back to you and used to discriminate against you or your family. State and federal laws provide some protections against genetic and pre-existing conditions discrimination.

Possible Other Risks

You may not donate blood at a blood bank while taking part in this study. You may not donate blood for one year after CAP256V2LS injection.

What are the risks related to pregnancy?

We do not know how the experimental mAb may affect a fetus or nursing infant. Therefore, women who can become pregnant must have a negative pregnancy test before product administration and agree to use effective birth control beginning at least 21 days before the first injection until the end of the study. We will discuss effective methods of birth control with you.

You must tell the clinic staff right away if you become pregnant, if your birth control method fails, or think that you might be pregnant during the study. You will be asked to continue with follow-up visits so that we can check your health. We will ask you the outcome of the pregnancy.

There are no known or anticipated effects of CAP256V2LS on sperm.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You will not benefit from being in this study.

Are there any potential benefits to others that might result from the study?

The study is not designed to protect you from HIV. We do not know if the mAb will work. You and others may benefit in the future from the information that will be learned from the study.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Instead of being in this study, you could choose not to take part. You may be eligible for other VRC studies.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

At each visit you will be checked for any health changes or problems. Blood will be drawn at almost every study visit to check on your health. You will be told right away, either by phone call or text if any of your test results show a possible health problem.

The results of this study may be reported in medical journals, on the internet or at scientific meetings. We will give you information about how to find the study results once they are available.

EARLY WITHDRAWAL FROM THE STUDY

You may be removed from the research study by the researcher for any of the following reasons:

- You don't keep appointments or follow study procedures;
- You get a serious illness that needs ongoing medical care;
- You become pregnant;
- You need to get treatment with a medication that affects your immune system (such as asteroid like prednisone).
- If the researcher believes that it is in your best interest to remove you from the study.
- The study is stopped by regulatory agencies, the study sponsor or study investigators. If this happens, we will tell you why.

If you agree to take part in this study, it is important for you to keep all of your appointments. Your participation in this study is completely voluntary. You can choose to stop taking part in the study at any time. There is no penalty or loss of benefits if you choose to leave the study.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

By agreeing to take part in this study, you give permission for your coded specimens and data to be stored and used for future research as described above.

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are like this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

If you change your mind and do not want us to use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee it. For example, if research with your specimens and/or data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee it. For example, if research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

By agreeing to take part in this study, you give permission for your coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. If we do this, we would not be

able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. Usually, these researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known, or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

PAYMENT

Will you receive any type of payment for taking part in this study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines. 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 thecompensation provided.

The compensation is $430 for a study visit that includes administration of CAP256V2LS. If enrollment occurs on a different day than study product administration, you will be compensated $200. You will get $25 total for the timely completion of all 7 days of an electronic diary. You will get $200 for each scheduled follow-up visit that includes a blood draw. You will get $85 for each follow up visit that does not include a blood draw.

If you are enrolled in Group 1, the total compensation for completion of all study visits is about $2655. If you are enrolled in Group 2, the total compensation for completion of all study visits is about $2855.

The total compensation you get is based on the number and type of study visits you complete. You will get the compensation about 2 weeks after each completed visit by direct deposit into a bank account that you specify to the Volunteer Payment Office.

If you are unable to finish the study, you will receive compensation only for the parts you completed. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year.

We will need your social security number to process your compensation. You can still take part in the study if you don't give us your social security number, but you might not be able to get your compensation.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines. This study does not offer reimbursement for, or payment of, travel, lodging or meals.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

CONFLICT OF INTEREST (COI)

The NIH reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and a VRC research team have developed CAP256V2LS being used in this study. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of CAP256V2LS.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor, Vaccine Research Center (VRC) or their agent(s)

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is

involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH 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 NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Richard Wu, M.D., [redacted] Other researchers you may call are: J[redacted] You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.