Protocol Title: VRC 609: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB091-00-AB (N6LS), Administered Intravenously or Subcutaneously with or without recombinant human hyaluronidase PH20 (rHuPH20) to Healthy Adults

NCT: 03538626

Documents:

- IRB-approved Protocol (v9.0 07OCT2022) - Statistical Analysis Considerations located in Section 6 of the Protocol
- IRB-approved Main Informed Consent (v9.0 07OCT2022) - IRB approval date: 31OCT2022
- IRB-approved Supplementary Informed Consent (v8.0 07OCT2022) - IRB approval date: 31OCT2022

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VACCINE RESEARCH CENTER

Protocol VRC 609
(18-I-0105)

A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF A HUMAN MONOCLONAL ANTIBODY, VRC-HIVMAB091-00-AB (N6LS), ADMINISTERED INTRAVENOUSLY OR SUBCUTANEOUSLY WITH OR WITHOUT RECOMBINANT HUMAN HYALURONIDASE PH20 (RHUPH20) TO HEALTHY ADULTS

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

Clinical Trial Sponsored by:
NIAID, VRC
Bethesda, Maryland

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NIAID, VRC
Bethesda, Maryland

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NIH Principal Investigator: Richard Wu M.D.
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NIAID
[redacted]

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ABBREVIATIONS

Abbreviation	Term
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine aminotransferase
AoU	Assessment of Understanding
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
bNAb	broadly-neutralizing human monoclonal antibody
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CL	clearance
Cmax	maximum concentration
CRS	cytokine release syndrome
DP	drug product
DS	drug substance
ECL	electrochemiluminescence
EDP	ENHANZE® Drug Product
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion; end of injection
F	bioavailability
FBS	Fetal Bovine Serum
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HA	hyaluronan
HCL	hydrochloric acid
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRPP	Human Research Protections Program
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation

Abbreviation	Term
IgG1	Immunoglobulin G1
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
LIMS	Laboratory Information Management System
MAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mcg	microgram
mg	milligram
mL	milliliter
mM, mmol	millimole
MO	medical officer
MSD	Meso Scale Discovery
N6LS	Antibody directed against the CD4-binding site of the HIV-1 envelope trimer
NHP	Non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH CC	National Institutes of Health Clinical Center
OHRP	Office for Human Research Protections
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PI	Principal Investigator
PK	pharmacokinetic
PSRT	Protocol Safety Review Team
PT	preferred term
Q	Inter-compartmental clearance
QA	quality assurance
PH20	posterior head protein 20
rHuPH20	recombinant human hyaluronidase PH20
SAE	serious adverse event
SC	subcutaneous
SHIV	simian-human immunodeficiency virus
SOC	system organ class
SOE	Schedule of Evaluation

Abbreviation	Term
SUSAR	serious and unexpected suspected adverse reaction
T½	half-life
TCR	tissue cross reactivity
Tmax	time of maximal concentration (Cmax)
TMB	3,3',5,5'-Tetramethylbenzidine
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UP	unanticipated problem
USP	United States Pharmacopeia
Vd	volume of distribution
VIP	Vaccine Immunology Program
VRC	Vaccine Research Center
WBC	white blood cell
β-HCG	human chorionic gonadotropin
λz	terminal slope of concentration vs time profile

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

VRC 609: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB091-00-AB (N6LS), Administered Intravenously or Subcutaneously with or without recombinant human hyaluronidase PH20 (rHuPH20) to Healthy Adults

I, the Principal Investigator for the study site indicated above, agree to conduct the study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct the study in compliance with United States (US) Health and Human Services (HHS) regulations (45CFR 46); applicable US Food and Drug Administration (FDA) regulations; standards of the International Conference on Harmonization Guidelines for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee (IRB/EC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health) and institutional policies. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed.

I agree to maintain all study documentation pertaining to the conduct of this study, including but not limited to, case report forms, source documents, laboratory test results, and medication inventory records, for at least 2 years following submission of a marketing application to FDA (21 CFR 312.62). If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the FDA is notified. The HHS protection of human subjects' regulations require that institutions retain records of IRB/EC activities and documentation of informed consent of subjects for at least 3 years after study completion (45 CFR 46). 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	NIH-Clinical Center Vaccine Evaluation Clinic
Name/Title of Principal Investigator	Study Site Name

_____	_____
Signature of Principal Investigator	Date

PRÉCIS

VRC 609: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB091-00-AB (N6LS), Administered Intravenously or Subcutaneously with or without Recombinant Human Hyaluronidase PH20 (rHuPH20) to Healthy Adults

Study Design: This is the first study in healthy adults of the N6LS monoclonal antibody (MAb). It is a dose-escalation study to examine safety, tolerability, dose, and pharmacokinetics (PK) of N6LS administered intravenously (IV) and subcutaneously (SC) to healthy adults. For SC administration, N6LS will be administered alone or coadministered with the permeation enhancer rHuPH20 enzyme. Primary hypotheses are that N6LS administration to healthy adults will be safe by the IV and SC routes, alone and with rHuPH20 coadministration. A secondary hypothesis is that all N6LS administrations will be detectable in human sera with a definable half-life.

Product Description: N6LS (VRC-HIVMAB091-00-AB) is a human MAb targeted to the HIV-1 CD4 binding site. It was developed by the VRC/NIAID/NIH and manufactured under current Good Manufacturing Practice (cGMP) regulations at the VRC Vaccine Pilot Plant operated under contract by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc., Frederick, MD. The product is provided as a sterile aqueous buffered solution in 10 mL glass vials at a concentration of 100 mg/mL and volume of 6.25 mL.

Each vial of ENHANZE™ Drug Product (EDP) contains 0.5 mL of rHuPH20 formulated at a concentration of 1 mg/mL (~110,000 U/mL rHuPH20). rHuPH20 is a tissue permeability modifier that depolymerizes hyaluronan (HA), increasing the dispersion of a substance into the subcutaneous space, which enables SC delivery of co-administered antibody (-ies) at higher dose volumes (e.g., >10 mL) that cannot be administered quickly without rHuPH20. EDP is manufactured by Ajinomoto Althea, Inc, (San Diego, CA) for Halozyme Therapeutics, Inc. (San Diego, CA) and is supplied in 2 mL glass vials as a sterile, single-dose, injectable liquid.

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

Study Plan: This open-label study includes 8 dose groups to assess N6LS alone given as a single IV infusion at the 5, 20, or 40 mg/kg dose level (Groups 1, 3,4); a single SC injection at the 5 mg/kg dose level (Group 2); or in 3 administrations, spaced 12 weeks apart by SC injection at the 5 mg/kg dose level (Group 5), or by IV infusion at the 20 mg/kg dose level (Group 6). Two additional groups will assess N6LS given as a single SC injection mixed with rHuPH20 (2000 U/mL) at 5 mg/kg (Group 7) or 20 mg/kg (Group 8) doses. Enrollment opened with Groups 1, 2 and 5; and was followed by the sequential activation of Groups 3, 4, and 6. With implementation of the two SC N6LS+ rHuPH20 arms as a protocol amendment, Group 7 will open first to accrual, followed by Group 8.

VRC 609 Study Schema

Group	Subjects	Study Products		Dosing Schedule		
		N6LS Dose & Route	rHuPH20 Dose	Day 0	Week 12	Week 24
1	3	5 mg/kg IV	-	X		
2	3	5 mg/kg SC	-	X		
3	3	20 mg/kg IV	-	X		
4	3	40 mg/kg IV	-	X		
5	5	5 mg/kg SC	-	X	X	X
6	5	20 mg/kg IV	-	X	X	X
7	5	5 mg/kg SC	2000 U/mL	X		
8	5	20 mg/kg SC	2000 U/mL	X		
Total	32*	* The expected enrollment is 32 subjects. Enrollment up to a total of 40 subjects is permitted if additional subjects are necessary for safety or PK evaluations.				

IV = Intravenous; SC = subcutaneous

Note: rHuPH20 and N6LS are mixed and administered by SC infusion. The dose of rHuPH20 is 2000 Units per mL relative to the N6LS dose volume.

Study Duration: Study participation will be approximately 24 weeks for subjects in Groups 1 to 4, 7 and 8; and 48 weeks for subjects in Groups 5 and 6.

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; a 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. N6LS Background

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

The VRC/NIAID is investigating clinical applications of broadly-neutralizing human monoclonal antibodies (bNAbs) that bind the HIV-1 envelope protein [2-5]. Such antibodies block infection of target cells *in vitro*, and have been shown to prevent infection of non-human primates (NHP) in *in vivo* models for HIV [6-8].Through advances in B-cell immunology utilizing single-cell cloning methods, next-generation sequencing, high throughput computational analysis techniques, and increased cell culture survivability procedures, an extensive group of HIV-1 bNAbs have been isolated. These include antibodies with specificities to the CD4 binding site (VRC01 [9], VRC07-523LS [5], 3BNC117 [10]); the high-mannose patch (10-1074 [11], PGT121 [12]); the V2 apex (PG9 [13, 14], PGDM1400 [12], CAP256.25 [15]); and the membrane-proximal external region (10E8 [3, 16]). Another HIV-1 specific bNAb identified as N6 was recently isolated from a patient with a 21-year known history of HIV-1 infection that was controlled in the absence of ART [2].

N6 was characterized for IgG germline identity, recombination, and somatic hypermutation changes, and compared extensively to other HIV-1 bNAbs for epitope/paratope mapping and neutralization breadth and potency [2]. Analyses showed N6 belongs to the VRC01 class of CD4 binding site-directed bNAbs, which block HIV infection by occluding the binding site for the cellular receptor CD4. VRC01 and many members of the VRC01 class are broadly cross-reactive, however N6 is the best in class to date [2]. N6 employs two novel mechanisms to achieve unprecedented breadth and potency. First, the angle at which N6 binds to the CD4 molecule is tilted relative to other MAbs in this class, enabling it to retain robust binding regardless of changes in the adjacent HIV envelop V5 loop (a region known to cause steric clashes, decreased binding capacity, and reduced neutralization breadth and potency). Secondly, mutations in the variable gp120 V5 loop that may diminish N6 contact are offset by increased contacts to the conserved D loop mediated by the addition of novel amino acid sequences within the antibody. Moreover, comparison ribbon structures of N6 and VRC01 show how mutations and insertions in HIV-1 gp120 that likely render VRC01 ineffective by inducing steric hindrances against certain HIV isolates are resolved by the positional changes exerted by N6 [2].

In order to improve the pharmacokinetics of N6, two amino acid substitutions (methionine to leucine and an asparagine to serine M428L/N434S, that collectively yielded N6LS) were

introduced within the C-terminus of the heavy chain constant region of N6 via site-directed mutagenesis to increase its binding affinity for the neonatal Fc-receptor (FcRn). Incorporation of the LS mutations did not affect the neutralization breadth or potency of N6LS compared to N6 [2]. Based on preclinical and clinical studies of passively administered VRC01LS and VRC07-523LS [8, 17, 18], the LS modification is expected to result in enhanced recirculation and longer plasma half-life of N6LS relative to the wild-type Ab.

N6LS is being developed for the prevention of HIV-1 infection in uninfected adults and for treatment of HIV-1 infection in infected adults. VRC 609 is the first-in-human study to evaluate the safety, tolerability, and pharmacokinetics of this antibody.

1.2. Recombinant Human Hyaluronidase PH20 (rHuPH20)

Recombinant human hyaluronidase PH20 (rHuPH20) enzyme optimizes the SC delivery of co-administered therapeutics by depolymerizing hyaluronan (HA) in the extracellular matrix of the SC space that normally serves to restrict bulk fluid flow. ENHANZE™ Drug Product (EDP) is an investigational ready to use injectable drug product that contains 1 mg/mL (110,000 U/mL) recombinant human hyaluronidase PH20 (rHuPH20). rHuPH20 is the active ingredient of the commercial product *Hylenex*® recombinant (hyaluronidase human injection), hereafter referred to as HYLENEX (150 U/mL of rHuPH20), which has been FDA-approved since 2005 for subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in subcutaneous urography for improving resorption of radiopaque agents. Product administration once limited to IV infusion because of volume limits, can now use rHuPH20 to facilitate SC injections with advantages such as reduced administration time, decreased number of individual injections at administration, and delivery of higher product dosages/dose volumes.

Published reports have shown additional beneficial effects of rHuPH20 when co-administered with a therapeutic agent (antibody, protein), such as improved absorption, increased bioavailability, and reduced pharmacokinetics (PK) variability of certain agents [19, 20]. Importantly, the local permeability barrier tissue changes induced by rHuPH20 are reversible within 24-48 hours after administration, without any inflammatory or histological changes [21].

This Phase 1 study will be the first to evaluate the safety, tolerability, and pharmacokinetics of N6LS coadministered with rHuPH20 by SC infusion in healthy adults.

1.3. Nonclinical Experience

1.3.1. N6LS

The N6/N6LS antibodies have been evaluated in pseudovirus neutralization assays to assess for breadth and potency against Clades A, B, C, and AG viruses; lipid and tissue cross-reactivity studies to assess for binding to antigenic determinants in a full panel of normal human and Sprague-Dawley rat tissues and selected tissues from neonatal human donors; and proof-of-concept immunotherapy studies of SHIV-infected rhesus macaques. Results showed N6 demonstrated superior neutralization and breath when assessed in parallel comparisons with a panel of HIV-specific bNAbs. Specifically, N6 was able to neutralize 98% of viruses within a 181-pseudovirus panel at an IC_{50} threshold of 50 mcg/mL and 96% at an IC_{50} threshold of 1

mcg/mL. N6 neutralized 16 of 20 VRC01-resistant pseudoviruses, further demonstrating its extraordinary neutralization breadth and potency [2]. Additionally, N6 neutralized 98% of pseudoviruses in an extended panel of 173 clade C pseudoviruses at an IC_{50} <50 mcg/mL and a median IC_{50} of 0.066 mcg/mL.

Lipid or tissue cross reactivity (TCR) studies have not shown any strong evidence of toxicologically relevant self-reactivity. Minimal binding of N6LS to cardiolipin and mild reactivity with Hep-2 cells were observed in vitro. Moreover, in an activated partial thromboplastin time assay, which is a surrogate assay used to detect phospholipid binding, N6LS-spiked sera did not have a prolonged activated thromboplastin time when compared to positive and negative controls. A single Good Laboratory Practice (GLP) TCR study using a full panel of normal human and Sprague-Dawley rat tissues and selected tissues from neonatal human donors showed only limited staining with N6LS: extracellular staining in vascular smooth muscle of the walls of hyalinized vessels in the human uterus and cytoplasmic staining in the root sheath of hair follicles in rat skin. No membrane specific binding was observed suggesting that there is no cross-reactivity of toxicologic concern. Overall, the cumulative N6LS binding profile to the antigenic determinants examined closely resembles that elicited by the VRC01 class of HIV-1 bNAbs.

Passive immunization of chronically simian-human immunodeficiency virus (SHIV)-infected rhesus macaques with N6LS resulted in transient viremia control, the extent and duration of which appeared to correlate with N6LS plasma levels and baseline plasma viremia levels before N6LS treatment.

A repeat dose single GLP toxicology study in male and female Sprague-Dawley rats was conducted to assess the safety of three repeat-dose administrations, 10 days apart of N6LS at three dose-levels (4, 40, or 400 mg/kg) intravenously or at two dose-levels (5 or 50 mg/kg), subcutaneously and to evaluate the toxicity and reversibility of adverse effects after a 35-day recovery period. The study also included a PK analysis through 56 days-post first product exposure to measure N6LS levels after passive immunization with low and high IV and SC antibody dosages. Please refer to the Investigator's Brochure (IB) for additional information.

1.3.2. rHuPH20

The specific nonclinical pharmacology, pharmacokinetic, and toxicity studies evaluating rHuPH20 are summarized in the rHuPH20 IB, Section 4.

1.4. Clinical Experience

1.4.1. N6LS

As of August 4, 2021, 27 subjects have enrolled into Groups 1-8. A total of 22 out of 23 subjects enrolled in Groups 1-6 received N6LS study product administrations and completed the protocol. One subject in Group 2 terminated the study after enrolling but prior to product administration. The N6LS product has been administered to 14 subjects by IV infusion and 12 subjects by SC injection. Unsolicited AEs were reported by 16/26 (62%) subjects that received N6LS, with the most frequent events of upper respiratory tract infection (URTI) reported by 6 subjects (23%) and diarrhea reported by 4 subjects (15%). All unsolicited events were mild or moderate in

severity except for one grade 3 diarrhea that began 4 days after administration, spontaneously resolved 2 days later, and was determined to be possibly related to N6LS.

Solicited systemic symptoms were reported in 4/14 (29%) subjects following IV administration and 3/12 (25%) subjects following SC administration. Symptoms reported after IV administration included 4 events of mild headache, 1 mild event each of malaise, chills, and nausea. Symptoms reported after SC administration included 1 mild event each of malaise, myalgia, headache, and nausea. No fevers occurred after IV or SC administration.

Solicited local symptoms reported included moderate bruising (1/14 subjects, 7%) following IV administration. Solicited local symptoms after SC administration included mild pain/tenderness (9/12 subjects, 75%), mild to moderate swelling (4/12 subjects, 33%), mild to severe redness 6/12 subjects, 50%), and mild pruritus (3/12 subjects, 25%).

A study pause occurred on 7/23/2021 after criteria for a pause was met due to two Grade 3 injection site erythema events not resolving during the solicited diary card reporting period. A Group 7 (5 mg/kg SC N6LS + 2000 U rHuPH20/mL) subject developed injection site erythema to a maximum diameter of 13 cm which resolved after 30 days. A Group 8 (20 mg/kg SC N6LS + 2000 U rHuPH20/mL) subject developed injection site erythema to a maximum of 20 cm which resolved after 7 days. Since the episodes of Grade 3 erythema observed in both individuals were well tolerated, not accompanied by any other symptoms or lab abnormalities that would indicate potential systemic toxicity, and resolved without clinical sequelae, the erythema was judged to not represent an increased safety risk for study participants. Therefore, the study pause was lifted on 7/28/2021. In addition, the PSRT determined that the protocol would not need to be paused for future events of the same type and severity.

Data cleaning and analysis are currently ongoing for Groups 7 and 8 in preparation for the database lock.

Additional clinical experience is derived from other bNAbs such as VRC01, VRC01LS, and VRC07-523LS, with reactivity to the CD4-binding site of the HIV envelop protein and administered at the same doses, dose-schedules, and routes proposed in this study in healthy adults [9, 18, 22, 23]. Overall, Phase 1 and 2 trials with VRC MAbs have shown they are generally well-tolerated, with no deaths or serious adverse events assessed as related by the Sponsor reported. Local reactogenicity observed with IV administration of CD4-binding site mAbs to adults has included pain/tenderness, bruising, swelling, and localized erythema at the site of infusion that resolved within a few minutes to a few hours after the administration. Most participants reported no systemic reactogenicity symptoms with VRC01 IV administration; when observed, systemic solicited symptoms were of mild or moderate severity, started 1-3 days after administration of study product and lasted 1-2 days, with malaise/fatigue, myalgias, headaches and mild nausea being most common. There have been no severe solicited reactogenicity symptoms related to VRC01 IV injections.

SC administration of CD4-binding site mAbs has been well tolerated in adults and infants. Most study participants had either no local reactogenicity or local symptoms limited to injection site pain and/or tenderness, redness, and mild localized pruritus (itchiness). Most local symptoms resolve within the first days after product administration. In some cases moderate to severe erythema at the injection site have lasted up to six weeks post product administration before resolving without clinical sequelae.

Preliminary N6LS PK data showed the maximum serum concentrations (Cmax) occurred within the first few hours after IV administration, and approximately 6 days following SC administration. The mean (±SD) Cmax values after a single administration of N6LS were 28±10 µg/mL for the 5 mg/kg SC dose, 101+23 µg/mL for the 5 mg/kg IV dose, 589±236 µg/mL for the 20 mg/kg IV dose, and 1717±51 µg/mL for the 40 mg/kg IV dose.

Preliminary mean (±SD) C_{28D} serum concentrations after the first administration of N6LS were 15±6.1 µg/mL, 32±2.3 µg/mL, 96±25.4 µg/mL, and 43±1.3 µg/mL for the 5 mg/kg SC, 5mg/kg IV, 20 mg/kg IV, and 40 mg/kg IV doses, respectively.

1.4.2. rHuPH20

As of December 2021, 1,592 subjects were exposed to HYLENEX and other rHuPH20 drug products in 30 clinical studies conducted under IND 66,888, or in post-marketing Phase 4 studies. In partnered trials with co-administered therapeutics, more than 9000 subjects were exposed. Individual doses of rHuPH20 ranged from 15 to 96,000 U (See rHuPH20 IB, section 5.1).

Across all Halozyme-sponsored studies, SC injections of rHuPH20 have been well-tolerated in healthy subjects, dehydrated pediatric subjects, hospice and palliative care subjects, subjects with type 1 and 2 diabetes, and subjects with rheumatoid arthritis. SC injections of rHuPH20 alone or in combination with hydration fluids (Lactated Ringer's, normal saline), co-injected small molecules (morphine, ceftriaxone, ondansetron), peptides (insulin, and insulin analogs), and proteins (IgG and adalimumab) have been well-tolerated in all clinical trials [21, 24]. Most AEs were mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection site reactions, which have occurred less frequently, include burning, erythema, pain, and numbness. Mild-to-moderate headache was also commonly reported.

rHuPH20 is currently co-formulated with four approved anticancer therapies, trastuzumab (HERCEPTIN HYLECTA™/Herceptin® SC) PHESGO™ (pertuzumab/trastuzumab), Darzalez FASPRO™ (daratumumab), and rituximab (i.e., RITUXAN HYCELA®/RITUXAN® SC/MabThera® SC) and dosed sequentially with human immunoglobin to treat primary immunodeficiency (HyQvia®/HYQVIA®).

1.5. Rationale for the Study Design

Animal and *in vitro* models of HIV infection have suggested bNAbs reactive to antigenically diversified Env proteins expressed by quasispecies of circulating virus may hold significant promise as immunoprophylactic and/or therapeutic agents to thwart the subversive effects of HIV on the immune system. N6LS can mediate extraordinary breadth and potency against various HIV isolates, including strains traditionally resistant to other antibodies in this class. Moreover, its potency may indicate less antibody is required to mediate an effect, offering the possibility of subcutaneous administration as a more feasible approach to immunoprophylaxis. The introduction of the LS site-directed mutation to increase FcRn binding affinity is postulated to result in increased antibody half-life and persistence at biologically higher concentrations in the plasma, as was shown for VRC01LS and VRC07-523LS [8, 17, 18].

This study is the first-in-human trial to evaluate the safety of a single- or three, repeat-dose regimen of N6LS administered intravenously or subcutaneously. The study will also evaluate the feasibility of larger SC dose volumes (>2.5 mL) of N6LS administration facilitated by rHuPH20. The dosages selected for evaluation of N6LS are based on prior experience with another CD4-binding site antibody VRC01, which was shown in two clinical trials (VRC 601 and VRC 602 [22, 23]) to be safe and well-tolerated at 5-40 mg/kg dosages given intravenously and at a 5 mg/kg dosage given subcutaneously in both HIV-infected and -uninfected adult populations. While Groups 1 through 4 will receive a single dose of N6LS by SC injection or IV infusion, Groups 5 and 6 will be administered three-repeat doses of N6LS at 12-week intervals (i.e., on Weeks 0, 12, and 24). A 12-week interval for repeat-dosing has been used in clinical trials with VRC01LS [18] and VRC07-523LS [25]. Groups 7 and 8 will receive a single 5 or 20 mg/kg dose of N6LS co-mixed with rHuPH20 by SC infusion (Refer to the pharmacy manual for study product preparation and administration instructions). Aligning the antibody dose levels and administration interval with that used in the current and prior studies with other HIV-1 bNAbs will allow for a direct comparison of the serum concentration of each bNAb at identical time-points. This in turn will support pharmacokinetic (PK) profile comparisons and characterization of the bNAbs currently in development by the VRC. The PK of N6LS administered using different regimens, dosages, and routes is also being evaluated in healthy adults aged 18 to 50 years.

1.6. Research-specific Laboratory Assessments

The research assays described in this section are designed to characterize the investigational product rather than assess the health of the subjects. Laboratory assessments in this Phase 1 study will include PK analysis, evaluation for anti-drug antibody (ADA) development following product exposure, and ex vivo analysis to assess the neutralization activity of N6LS post-injection/infusion.

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.

1.6.1. Pharmacokinetic (PK) Analysis

The N6LS concentration for the PK analysis will be measured by a Meso Scale Discovery (MSD) or similar assay [22].

1.6.2. Anti-drug Antibody (ADA) Analysis

A three-level algorithm will be used to screen, confirm, and functionally characterize ADA to N6LS and rHuPH20 in clinical serum and plasma samples collected at baseline (day 0), Week 4 (Day 28), and Week 8 (Day 56) for groups 1-4, and Groups 7-8. For groups 5-6, ADA is

analyzed at baseline (Day 0), Week 4 (Day 28), Week 28 (Day 196), and Week 32 (Day 224). Analysis will be conducted according to the Food and Drug Administration (FDA) guidance [26]. Screening and confirmation will involve a Meso Scale Discovery (MSD) electrochemiluminescence (ECL) bridging or similar assay [22].

Tier 1 and 2 N6LS ADA assays are qualified and method development to functionally characterize ADA activity in clinical serum samples that also contain N6LS (tier 3 assay) is ongoing and not presently available. However, the stored clinical serum samples will be tested once the assay is qualified.

1.6.3. HIV Pseudovirus Neutralization

For all study groups, subject sera collected (but not limited to) at baseline (Day 0), 48 hours post-administration, and at Day 84 may be evaluated to assess the functional capacity of passively administered N6LS to neutralize pseudotyped HIV viruses using an *in vitro* cell-based virus neutralization assay such as previously described for VRC01, VRC01LS, and VRC07-523LS [2, 22, 23, 25, 27].

1.6.4. 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 N6LS antibody half-life or an ADA response [28-30]. Coded stored samples will be used for evaluation of the genetic sequence of the immunoglobulin heavy chain constant region allotype.

2. INVESTIGATIONAL PRODUCTS

This protocol will evaluate the use of two investigational products: the antibody N6LS and rHuPH20, the active pharmaceutical ingredient in EDP. A summary of the manufacturing process for N6LS is provided in this section. Please refer to the rHuPH20 IB, Section 3 for additional information on rHuPH20 and EDP. Refer to the pharmacy manual for product preparation and administration guidance.

2.1. N6LS (VRC-HIVMAB091-00-AB)

2.1.1. Overview

The N6LS antibody binds to the CD4-binding site of HIV-1 gp120 protein and contains a methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as (LS) change within the C-terminus of the heavy chain constant region to increase its binding affinity for the neonatal Fc receptor (FcRn) [31]. The antibody is expressed as a recombinant IgG1 antibody in a Chinese Hamster Ovary (CHO) mammalian cell line, CHO-DG44, and is manufactured under current Good Manufacturing Practices (cGMP) by VRC/NIAID/NIH at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program, Leidos Biomedical Research, Inc., Frederick, MD. Specific manufacturing information is included in the IB. Quality Assurance (QA) lot release testing by the manufacturer and ongoing stability programs verify the continued conformance to product specifications and justification of use prior to, and during conduct of the clinical trial.

2.1.2. Manufacturing and Drug Product Production

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

The N6LS DS is diluted to a concentration of 100 mg/mL in formulation buffer composed of 10 mM Sodium Citrate, 50 mM Sodium Chloride, 150 mM Arginine-HCl, and 0.002% Polysorbate-80 (PS-80) at pH 6.5 to generate the drug product (DP). The product is filled into 10 mL single-use glass vials at a concentration of 100 ± 10 mg/mL and volume of 6.25 ± 0.10 mL. The drug product (DP) should be stored at -35°C to -15°C.

More details on the N6LS composition and manufacturing can be found in the IB.

2.2. ENHANZE™ Drug Product (EDP)

Recombinant human hyaluronidase PH20 (rHuPH20) is the active ingredient of the investigational ENHANZE™ Drug Product (EDP). rHuPH20 is produced by genetically engineered Chinese hamster ovary (CHO) cells containing a deoxyribonucleic plasmid encoding a soluble fragment of human hyaluronidase PH20. The purified hyaluronidase glycoprotein contains 444-447 amino acids with an approximate molecular weight of 61,000 Daltons.

EDP, manufactured by Ajinomoto Althea, Inc. (San Diego, CA) for Halozyme, Inc. (San Diego, CA), is a purified preparation of rHuPH20 supplied in glass vials as a sterile, clear, colorless, non-preserved, ready-for-use solution. Each mL contains ~110 kU of rHuPH20. The solution has a pH of approximately 6.5 and contains 130 mM sodium chloride, 10 mM L-histidine hydrochloride as a buffer, and 10 mM L-methionine, 0.02% w/w PS80. The solution is filled to 0.5 mL in a 2 mL glass vial and should be stored as labeled, either at -20°C ± 5°C or 5°C ± 3°C and protected from light.

More details on rHuPH20 and EDP are provided in the rHuPH20 IB (Edition 10.0, February 04, 2022).

3. STUDY OBJECTIVES

3.1. Primary Objectives

- To evaluate the safety and tolerability of N6LS administered as a single dose at 5 mg/kg IV, 20 mg/kg IV, 40 mg/kg IV, or 5 mg/kg SC to healthy adults.
- To evaluate the safety and tolerability of N6LS administered at 5 mg/kg SC or 20 mg/kg IV by repeat dosing every 12 weeks for a total of 3 injections/infusions in healthy adults.
- To evaluate the safety and tolerability of a single 5 or 20 mg/kg SC dose of N6LS coadministered with rHuPH20 in healthy adults.

3.2. Secondary Objectives

- To evaluate the pharmacokinetics of N6LS at each dose level through 24 weeks after the last dose.
- To determine whether anti-drug antibody (ADA) to N6LS can be detected in sera of N6LS recipients at specific timepoints throughout the study.

3.3. Exploratory Objectives

- To evaluate for evidence of functional activity of N6LS in samples collected during the study at specific timepoints.
- To assess for IgG1 allotypes by polymerase chain reaction (PCR) and evaluate for allotype-specific effects on N6LS pharmacokinetics.

4. STUDY DESIGN AND CLINICAL PROCEDURES

This is an open-label, dose-escalation study to examine the safety, tolerability, dose, and PK of N6LS in healthy adults. As shown in the study schema in Table 1, subjects in Groups 1 to 4 will receive a single dose of N6LS at the 5, 20, or 40 mg/kg dose level; subjects in Groups 5 and 6 will receive repeat dosing of N6LS every 12 weeks for a total of 3 injections at the 5 mg/kg dose level or 3 infusions at the 20 mg/kg dose level, respectively; subjects in Groups 7 and 8 will receive a single dose of N6LS at the 5 mg/kg and 20 mg/kg dose level (respectively) co-administered with rHuPH20 (2000 U/mL) via SC infusion.

If enrolled into Groups 1, 4, 7 and 8 subjects will be expected to be available for follow-up visits through 24 weeks of study participation. Subjects enrolled into Groups 5 and 6 will be expected to be available for follow-up visits through 48 weeks of study participation.

Table 1: VRC 609 Study Schema

Group	Subjects	Study Products		Dosing Schedule		
		N6LS Dose and Route	rHuPH20 Dose	Day 0	Week 12	Week 24
1	3	5 mg/kg IV	-	X		
2	3	5 mg/kg SC	-	X		
3	3	20 mg/kg IV	-	X		
4	3	40 mg/kg IV	-	X		
5	5	5 mg/kg SC	-	X	X	X
6	5	20 mg/kg IV	-	X	X	X
7	5	5 mg/kg SC	2000 U/mL	X		
8	5	20 mg/kg SC	2000 U/mL	X		
Total	32*	* A total of 32 subjects are planned for enrollment. However, up to 40 subjects may be enrolled to replace subjects who fail to complete the assigned dosing regimen and to meet requests for additional pharmacokinetic (PK) and/or new safety evaluations.				

IV = Intravenous; SC = subcutaneous

Note: rHuPH20 and N6LS are mixed and administered by SC infusion. The dose of rHuPH20 is 2000 Units per mL relative to the N6LS dose volume. Refer to the pharmacy manual for study product preparation and administration instructions.

Enrollment began with the 5 mg/kg dose groups (Groups 1, 2, and 5) when the protocol opened to accrual. Enrollments into the subsequent dose groups (Groups 3, 4, and 6) proceeded after dose-escalation reviews as described in Section 4.3. With implementation of the two N6LS+ rHuPH20 groups as a protocol amendment, Group 7 will open first to accrual, followed by Group 8 pending a dose-escalation review. For each dose level and administration route with or without rHuPH20, the study team will wait at least 3 days following the first product administration before the same dose and administration route of N6LS is administered to additional subjects. Safety review decisions and the status of the enrollment process will be transparent to the Protocol Safety Review Team (PSRT) throughout the trial and discussed

during the weekly and/or monthly safety review. The composition of the PSRT is discussed in Section 8.8.

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

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

4.1. Study Population

All inclusion and exclusion criteria must be met for eligibility.

4.1.1. Inclusion Criteria

A subject must meet all of the following criteria:

1. Willing and able to complete the informed consent process.
2. 18 to 50 years of age.
3. Based on history and examination, must be in good general health and without history of any of the conditions listed in the exclusion criteria.
4. Willing to have blood samples collected, stored indefinitely, and used for research purposes.
5. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process.
6. Screening laboratory criteria within 84 days prior to enrollment must meet the following criteria:
    - White blood cell count (WBC): 2,500-12,000/mm^3.
    - WBC differential: Within institutional normal range or accompanied by the Principal Investigator (PI) or designee approval.
    - Platelets: 125,000 – 400,000/mm^3.
    - Hemoglobin: Within institutional normal range or accompanied by PI or designee approval.
    - Creatinine: ≤ 1.1 x Upper Limit of Normal (ULN).
    - ALT: ≤ 1.25 x ULN.
    - AST: ≤ 1.25 x ULN.
    - Negative for HIV infection by an FDA approved method of detection.

Female-Specific Criteria:

7. If a woman is of reproductive potential and sexually active with a male partner, then she agrees to use an effective means of birth control from the time of study enrollment until the last study visit, or to be monogamous with a partner who has had a vasectomy.

8. Negative β-HCG (human chorionic gonadotropin) pregnancy test (urine or serum) on day of enrollment for women presumed to be of reproductive potential.

4.1.2. Exclusion Criteria

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

1. Prior receipt of licensed or investigational monoclonal antibody.
2. Weight > 115 kg.
3. Any history of a severe allergic reaction with generalized urticaria, angioedema or anaphylaxis within the 2 years prior to enrollment that has a reasonable risk of recurrence during the study.
4. Hypertension that is not well controlled.
5. Woman who is breast-feeding, or planning to become pregnant during the study participation.
6. Receipt of any investigational study agent within 28 days prior to enrollment.
7. Any other chronic or clinically significant medical condition that in the opinion of investigator would jeopardize the safety or rights of the subject including (but not limited to): diabetes mellitus type I, chronic hepatitis; OR clinically significant forms of drug or alcohol abuse, asthma, autoimmune disease, infectious disease, psychiatric disorders, heart disease, or cancer.
8. Known hypersensitivity to hyaluronidase or any of the excipients in EDP.

4.2. Inclusion of Vulnerable Subjects

4.2.1. Participation of Children

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

4.2.2. Participation of NIH Employees

NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the "NIH FAQs for NIH Staff Who are Considering Participation in NIH Research " published by Office of Human Research Subjects Protections on Research Involving NIH Staff as Subjects, Policy 404.

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

- Informed that neither participation nor refusal to participate as a research subject will have an effect, either beneficial or adverse, on the subject's employment, training or position at the NIH,
- When possible, consent should be obtained by an individual in a non-supervisory relationship with the subject, and

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

4.2.3. Adult Subjects who Lack the Capacity to Consent

Adults who are unable to provide initial informed consent are not eligible to enroll. Also, adults who permanently lose the capacity to provide on-going consent after initial consent and during the study will be discontinued from protocol participation as it is described in Section 4.5

4.3. Clinical Procedures and Laboratory Assays

Evaluation of study product safety for this study will include laboratory studies, medical history, and physical assessment by clinicians, and subject self-assessment on a diary card for 3 days after product administration. The study schedule is provided in the Schedule of Evaluations, Appendix I. Total blood volume drawn from each subject will comply with the NIH CC Guidelines, which is available on the NIH intranet at the following link: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf.

4.3.1. Recruitment and Retention Strategies

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

4.3.2. Screening

All screening procedures for this study are described and will be completed through the Vaccine Research Center's screening protocol, VRC 500 (NIH 11-I-0164) used for all VRC IND studies conducted at the NIH Clinical Center. The Recruitment Plan per NIH Policy 302 for all VRC studies can be found in the NIH IRB approved VRC 500 protocol. Subjects will be recruited through Institutional Review Board (IRB)-approved advertising. Screening evaluations performed to determine eligibility for study participation will include medical history review, physical exam, and the clinical laboratory tests as detailed in the Schedule of Evaluations, Appendix I). No screening procedures will be done under protocol VRC 609.

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

Blood samples for research can be drawn at any time during the screening period and are not required to be repeated if outside the screening period. Informed consent documents will be

reviewed. Counseling related to potential risks of the study product, pregnancy prevention and HIV risk-reduction will be performed. An Assessment of Understanding (AoU) will be completed in association with enrollment into VRC 609. Screening records will be kept to document the reason why an individual was screened but not enrolled.

4.3.3. Enrollment, Study Days and Visit Numbers

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

Day 0 is defined as the day of first N6LS administration. Day 0 may occur on the same day as enrollment or up to 6 weeks after enrollment. This period may be increased with PI approval. If Day 0 does not coincide with enrollment, then the enrollment day may be referred to by a negative number of days (i.e., Day -1 to Day -42). For calculating elapsed days following Day 0, each subsequent calendar date is labeled by the next sequential "Study Day" as shown in the Schedule of Evaluations (Appendix I). Since there may be more than one research sampling timepoint of interest per study day, each sample collection timepoint has its own "Visit Number." For this reason, there may be more than one visit number recorded on the same calendar date.

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

4.3.4. Administration of N6LS

All study product administrations will be completed according to the assigned group. For women of childbearing potential, a negative pregnancy test must be obtained prior to product administration that day. Refer to the pharmacy manual for study product preparation and administration instructions.

Prior to each product administration, temperature, blood pressure, heart rate (pulse) and weight will be recorded and a targeted physical examination will be conducted. All subjects will be observed for 4 hours after the first product administration. Subjects in the multi-dose groups will be observed for at least 2 hours after the second and third product administrations.

IV Administration

If a subject is assigned to an IV administration group, the IV access will be placed in an arm vein in an aseptic manner. A different site may be used for collection of PK blood samples; however, the same site may be used after flushing the line if another site is not available. N6LS will be administered with approximately 100 mL of normal saline IV (as described in the IB) over about 15-30 minutes, with a target of 30 minutes for the initial infusion for each subject. 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.

SC Administration without rHuPH20

If a subject is assigned to a SC administration group, the SC administration site(s) to be used must be assessed as acceptable by the clinician and the subject. The preferred SC administration

site is the abdomen, but the upper arm or thigh may be used. Given the weight criterion in this study, the maximum volume needed to administer a 5 mg/kg SC dose is not expected to exceed 5.75 mL. The SC dose will be administered by standard needle in a maximum volume of about 2.5 mL per injection site. Up to 4 SC injection sites may be used if deemed necessary by the clinician. SC administration sites should be at least 2 inches apart.

SC Administration with rHuPH20

If a subject is assigned to a SC administration group, the SC administration site(s) to be used must be assessed as acceptable by the clinician and the subject. The preferred SC administration site is the abdomen. N6LS will be mixed with **rHuPH20** in the pharmacy and then administered via standard Medfusion 3500 syringe pump (or equivalent) in one infusion site at a rate of no more than 3 mL/minute. Given the weight criterion in this study, the maximum volume needed to administer a 20 mg/kg SC dose is not expected to exceed 23.42 mL. If the subject experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate the symptoms. Procedures for all N6LS preparations and administrations are described in Section 7.

4.3.5. Solicited Adverse Events and Clinical Follow-up

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

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

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

Clinical laboratory assays and clinical evaluations will assess safety and tolerability at specified intervals after each administration. Throughout the study, clinicians will also assess subjects for

any changes in symptoms. Any new or concerning symptoms will be fully assessed to include specialty consultation at the NIH Clinical Center as indicated clinically.

4.3.6. Pharmacokinetics

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

4.3.7. Schedule of Evaluations

The Schedule of Evaluations (Appendix I) provides details on the study schedule and the permitted visit windows. Schedule 1 is for the IV dose escalation groups receiving one infusion (Groups 1, 3, and 4). Schedule 2 is for the SC dose group receiving one injection (Group 2). Schedule 3 and Schedule 4 are for the groups receiving repeat dosing: Group 5 (5 mg/kg SC) and Group 6 (20 mg/kg IV), respectively. Schedule 6 is for the N6LS+ rHuPH20 SC dose groups receiving one infusion at N6LS dose levels of 5 mg/kg (Group 7) or 20 mg/kg (Group 8). After enrollment, deviations from the visit windows are discouraged but will be permitted at the discretion of the PI or designee; and will be recorded as protocol deviations.

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

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

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

4.3.8. Concomitant Medications

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

4.4. Criteria for Dose-Escalation and Repeat-Dosing

Dose groups will be enrolled sequentially in a staged manner, depending on the outcome of planned PSRT Data Reviews. These reviews will determine if dose-escalation to the next higher N6LS dose level may occur, and if 2nd and 3rd doses (repeat-dosing) may be administered to applicable dose groups (Table 2). Whenever possible and as data are available, PSRT Data Reviews for dose-escalation and repeat-dosing will be held concurrently as follows:

Table 2: Schema for Dose-escalation and Repeat-Dosing PSRT Data Reviews

Data Review Objective	Minimum Evaluable Safety Data*	Favorable Review Outcome
Review #1		
• Dose-escalation from 5 to 20 mg/kg IV • Repeat-dosing at 5 mg/kg SC	• All post-administration safety data from Day 0 through at least the "Day 14" visit in at least 3 subjects in Group 1. • All post-administration safety data from Day 0 through at least the "Day 14" visit in at least 3 subjects in Group 2 or 5.	• Proceed with enrollments into Groups 3 and 6. • Proceed with second and third doses in Group 5.
Review #2		
• Dose-escalation from 20 to 40 mg/kg IV • Repeat-dosing at 20 mg/kg IV	• All post-administration safety data from Day 0 through at least the "Day 14" visit in at least 3 subjects in Group 3 or 6.	• Proceed with enrollments into Group 4. • Proceed with second and third doses in Group 6
Review #3		
• Dose-escalation from 5 to 20 mg/kg N6LS with rHuPH20 by SC infusion	• All post-administration safety data from Day 0 through at least the "Day 14" visit in at least 3 subjects in Group 7	• Proceed with enrollments into Group 8.

If the first product administration is not completed or there are discontinuations from the study before there are sufficient data to conduct the dose escalation review, then extra subjects may be enrolled in order to have the requisite data on at least 3 subjects at the dose level and route being evaluated. Additionally, AEs assessed as related to the study product at the time of a dose-escalation review may be judged by the PSRT to warrant adding additional subjects at a given dose group.

The IRB will be provided with documentation of the safety review process and notification of the dose-escalation. Consultation with the IRB and notification of the FDA, if needed, as per study pause criteria (Section 4.6) will occur if indicated by the review. One outcome of a dose-escalation review may be to recommend evaluation of additional subjects at the current dose and reassess for safety before proceeding to a higher dose.

4.5. Criteria for Subject Discontinuation from Protocol Participation

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

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

4.6. Criteria for Discontinuation of N6LS or N6LS+ rHuPH20 Administration

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

- Pregnancy (female subjects only);
- Grade 3 adverse event assessed as related to N6LS or N6LS+rHUPH20 (with the exception that self-limited Grade 3 solicited reactogenicity will not require discontinuation of product administration);
- Grade 4 adverse event assessed as related to N6LS or N6LS+rHUPH20;
- Immediate hypersensitivity reaction associated with N6LS or N6LS+rHUPH20;
- Intercurrent illness that is not expected to resolve prior to the next scheduled study product administration AND for which PI (or designee) believes is in the best interest of the subject to restrict further exposure;
- Repeated failure to comply with protocol requirements;
- Co-enrollment into a study to receive another investigational research product prior to completion of the requisite study follow-up following the last N6LS product administration;
- The IND sponsor or the study PI decide to terminate the study;
- The IRB, Office for Human Research Protections (OHRP) or the FDA halt the study.

Subjects who have received at least one dose of N6LS but have been discontinued from further study product administrations, will continue with follow-up as shown in the Schedule 5 of the SOE with the exception that research sample collections will be discontinued for pregnant women or others in which it is contraindicated.

4.7. Criteria for Pausing and Resuming the Study

Administration of either study product (N6LS or N6LS+ rHuPH20) and new enrollments will be paused by the PI if any of the following criteria is met:

- **One** (or more) subject experiences a serious adverse event **(SAE)** that is assessed as related (possible, probably, or definitely) to the study product, or

- **Two** (or more) subjects experience the same **Grade 3 or higher AE** that is assessed as related (possible, probably, or definitely) to study agent (other than self-limited Grade 3 AEs that resolve during the solicited reactogenicity period).

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

Plan for Review of Pauses and Resuming Rules:

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

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

5. SAFETY AND ADVERSE EVENTS

5.1. Adverse Events

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

Severity of AEs will be assessed using the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Even*ts, Corrected Version 2.1 [July 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf. Additional information can be found in Appendix II. This grading scale has been used in all prior studies with other HIV-1 bNAbs and will allow for a direct comparison of safety across all available HIV-1 bNAbs.

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

When a subject who receives N6LS coadministered with rHuPH20 experiences an AE assessed by the investigator as related to study product, this attribution reflects relatedness to N6LS and not rHuPH20. Any differences in safety and tolerability between the 5 mg/kg SC N6LS dose without rHuPH20 and 20 mg/kg N6LS SC dose with rHuPH20 will be interpreted as a dose-response difference of N6LS delivered subcutaneously. The extant experience with rHuPH20 indicates that rHuPH20 itself does not confer a unique set of AEs and this protocol will not specifically evaluate rHuPH20 itself for safety and tolerability.

5.2. Serious Adverse Events

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

“Life-threatening” refers to an AE that at occurrence represents an immediate risk of death to a subject. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. Similarly, a hospital admission for an elective procedure is not considered a SAE.

5.3. Adverse Event Reporting to the IND Sponsor

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

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

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

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

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

5.4. IND Sponsor Reporting to the FDA

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

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

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

The IND Sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.32.

5.5. Reporting to the Institutional Review Board

The following information is consistent with NIH IRB Policy 801: Reporting Research Events, Version 1, effective July 1, 2019.

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

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

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

5.5.1. Unanticipated Problem (UP) Definition

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

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

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

5.5.2. Non-Compliance Definition

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

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

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

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

the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different noncompliant events.

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

5.5.3. Protocol Deviation Definition

A protocol deviation is defined as any change, divergence, or departure from the IRB-approved research protocol and is further characterized as major and minor as follows:

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

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

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

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

5.5.4. Death

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

5.5.5. New Information

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

5.5.6. Suspension or Termination of Research Activities

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

5.5.7. Expedited Reporting to the IRB

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

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

- Actual or suspected UPs;
- Actual or suspected non-compliance;
- Actual or suspected Major PDs;
- SAEs that are actual or suspected UPs;
- New information that might affect the willingness of a subject to enroll or remain in the study;

Suspension or termination of research activities, including holds on new enrollment, placed upon the research by the study sponsor, NIH or IC leadership, or any regulatory agency.

5.5.8. Annual Reporting to the IRB

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

- Summary of UPs and non-compliance;
- AEs, including SAEs, that are not UPs, as a narrative summary statement indicating whether these events were within the expected range;
- Minor PDs (aggregate summary);

Any trends or events which in the opinion of the investigator should be reported

6. STATISTICAL CONSIDERATIONS

6.1. Overview

This is a phase I dose-escalation study in healthy adults to assess the safety and pharmacokinetics of N6LS (VRC-HIVMAB091-00-AB), a human monoclonal antibody with broad HIV-1 neutralizing activity, with or without rHuPH20. Recruitment will target about 32 healthy adults, 18 to 50 years of age, as shown in Table 1. The permitted accrual is 40 subjects in total to allow for additional enrollments in the event that an enrolled subject does not complete the minimum evaluations needed to meet the protocol criteria for the group dose safety or dose-escalation evaluation. Dose escalation rules are described in Section 4.3.

6.1.1. Treatment Assignments

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

6.2. Sample Size Considerations

Although the study is primarily descriptive, the primary goal is to identify safety concerns associated with different N6LS dosages in group sizes ranging from 3 to 5 subjects. For a group size of 3 subjects, there is a 90% chance of observing at least 1 SAE if the true event rate is ≥ 0.536 and a 90% chance of observing no SAE if the true event rate is ≤ 0.034. For a group size of 5 subjects, there is a 90% chance of observing at least SAE if the true rate is ≥ 0.37 and a 90% chance of observing no event if the true rate is ≤ 0.02. The probabilities of observing 0 and 1 or more event are presented in Table 3 for a range of possible true event rates. These calculations provide a complete picture of the sensitivity of this study design to identify potential safety problems with the study agent. For example, within the group of size n=3, if the true event rate is 0.01, then there is a probability of 0.97 to observe no event and a probability of 0.03 to observe at least 1 event; while, within the group of size n=5, if the true event rate is 0.01, then there is a probability of 0.951 to observe no event and a probability of 0.05 to observe more than 1 event.

Table 3: Event Probabilities for Different Scenarios

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

Table 4 displays the upper and lower 95% exact binomial confidence bounds for all possible number of observed events in a group. For a group size of 3 subjects, the upper 95% exact confidence bound on the true rate is 0.708 if no events are observed; the lower bound will be 0.292 if all subjects experience the event. Likewise, for a group size of 5 subjects, the upper 95% exact confidence bound of the true rate is 0.522 if no events are observed; the rate of the lower bound is 0.478 if all subjects experience the event.

Table 4: 95% Confidence Intervals of the True Rate for All Possible Number of Observed Events within a Dose Group

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

Table 3 and Table 4 also apply to the secondary and exploratory objectives.

6.3. Statistical Analysis

6.3.1. Analysis Variables

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

6.3.2. Baseline Characteristics

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

6.3.3. Safety Analysis

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

Solicited Adverse Events:

Solicited AE data will be collected after each product administration. The number and percentage of subjects experiencing each type of solicited sign or symptom will be tabulated by severity and by dose group, select pooled groups (i.e., all IV dose groups, all 5 mg/kg SC dose groups (no rHuPH20), and all rHuPH20 dose groups), and overall (all dose groups). Subjects with multiple occurrences of the same event will be counted once using the event of highest severity.

Adverse Events:

All unsolicited AEs reported through 56-days post each product administration will be recorded and coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The number and percentages of subjects with each unsolicited AE will be tabulated by severity and relationship to the study product, by dose group, select pooled groups (i.e., all IV dose groups, all 5 mg/kg SC dose groups (no rHuPH20), and all rHuPH20 dose groups), and overall (all 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.

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.

6.3.4. Tolerability Evaluation

The tolerability of an investigational medicinal product represents the degree to which overt adverse effects can be tolerated by the subject [32]. Since VRC 609 will be the first trial of N6LS in healthy adults, the tolerability evaluation will include mostly descriptive summaries of the frequency of solicited AE reports with an onset in the 3 days following each N6LS administration and subject withdrawals or discontinuations based upon subject discomfort or AEs. This early assessment of tolerability to N6LS will inform the parameters to solicit or routinely assess in future studies to further characterize the tolerability profile in a larger subject cohort.

6.3.5. Pharmacokinetics Analysis

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

Individual Subject Pharmacokinetic Analysis: A non-compartmental PK analysis will be performed using Phoenix 7.0 (Certara^{R}) or a similar program on the N6LS concentration data generated from each subject. Calculated PK parameters for IV Groups 1, 3, 4, and 6 will include: area-under-the-curve (AUC), maximum concentration (C_{max}), time to C_{max} (T_{max}), clearance (CL), volume of distribution (Vd_z), terminal elimination rate constant (λ_z) and the terminal half-life ($T_{1/2}$). For Groups 2, 5, 7 and 8, the PK parameters will include AUC, C_{max}, T_{max}, apparent clearance (CL/F), apparent volume of distribution (Vd_z/F), λ_z and $T_{1/2}$. C_{max} and T_{max} will be taken directly from the observed concentration-time data. The terminal slope, λ_z, will be determined from the log-linear portion of the curve and the $T_{1/2}$ calculated as $0.693/\lambda_z$. AUC will be determined using the linear trapezoidal method through the Week 24 PK sample for single dose groups (1-4, 7 and 8) and through Week 48 for multiple dose groups (5 and 6) or through the last PK sample with a concentration above the quantitative limit. The AUC over the

first 12 weeks following the first dose ($AUC_{0\text{-}WK12}$) will be determined for all dose groups. If the final sample (C_{last}) has a measurable N6LS concentration, the remaining AUC after the final concentration ($AUC_{Clast\text{-}inf}$) will be estimated as C_{last}/λ_z. Data will be summarized by dose group and overall for IV administration groups for CL, Vd and $T_{1/2}$. For Groups 5 and 6, potential accumulation will be assessed as the ratios of the $AUC_{0\text{-}WK12}$ and C_{max} for the first and the third doses. The potential for non-linearity PKs among IV groups will be determined by comparing the dose-adjusted ratios for C_{max} and $AUC_{0\text{-}WK12}$ between IV groups. Additional compartmental analysis will be performed as warranted by the data.

Population Pharmacokinetic Analyses: Population PK analyses will be performed on the N6LS PK data following IV and SC administration to determine compartmental PK parameters with the PK program NONMEM version 7.3 or later (ICON^R). Based on prior PK studies of bNAbs, a two compartment model will be used to analyze the N6LS PK data. The population analysis will generate estimates for initial and final volumes of distribution (Vd_1 and Vd_2), inter-compartmental clearance (Q), CL and bioavailability (F). Individual subjects' empiric Bayesian PK parameter estimates will be generated using the NONMEM posthoc subroutine. Given the small subject numbers, the population PK analysis will include a limited exploratory covariate analysis to assess dosing and clinical factors as fixed effects associated with N6LS PK parameters. The three factors that will be evaluated are dose level (5 vs 20 vs 40 mg/kg) on CL Vd1, Vd2 and F; repeat dosing CL Vd_1, Vd_2, and F; and EPD co-administration on SC F and absorption rate.

The longer compartmental half-life, $T_{1/2beta}$ will be determined from CL, Vd_1, Vd_2 and Q using standard PK equations. Final model selection will be based on changes in the objective function and graphically by goodness of fit plots. The final population PK model will be assessed using bootstrap analysis. N6LS dosing strategies and their ability to achieve and maintain target N6LS concentrations will be performed using the final population PK model and Monte Carlo simulations with at least 5000 replicates.

6.3.6. Interim Analyses

Preliminary PK analyses may be done once per dose level as the data for each dose level is obtained. This may be performed before a dose group's PK data is complete and may only generate a subset of the final PK parameters. The interim analyses will be used to inform decisions about the dose levels to be administered in future studies with N6LS.

7. PHARMACY PROCEDURES

The dose groups and N6LS dosing schedule are shown in Table 1. Refer to the N6LS IB for further information about N6LS (VRC-HIVMAB091-00-AB) administered in the absence and presence of rHuPH20.

7.1. Study Product and Administration Regimen

N6LS (VRC-HIVMAB091-00-AB) is a clear, colorless to yellow liquid, sterile aqueous buffered solution that is essentially free of visible particles and is filled into 10 mL single-dose vials. Each vial contains a 6.25 ± 0.10 mL volume of N6LS at a concentration of 100 ± 10 mg/mL in formulation buffer composed of 10 mM Sodium Citrate, 50 mM Sodium Chloride, 150 mM Arginine-HCl, and 0.002% Polysorbate-80 (PS-80) at pH 6.5. Vials have a nominal fill volume of 6.25 mL to enable withdrawal up to 6.0 mL.

In calculating the dose to administer and number of vials to thaw, it should be assumed that the concentration is 100 mg/mL and that a volume of at least 6 mL can be withdrawn from a vial. In this trial, dose is limited or established based on subject weight. *For example*, for a subject weighing 115 kg (the upper limit per protocol eligibility) who receives the 40 mg/kg dose, the N6LS amount needed is calculated as follows: 115 kg x 40 mg/kg = 4600 mg of N6LS, which corresponds to 46 mL of the 100 mg/mL solution. Since each product vial contains at least 6 mL, 8 vials will be needed for the dose preparation for this subject.

Preparation of N6LS for IV administration will require a 100 mL bag of 0.9% sodium chloride, United States Pharmacopeia (USP) (normal saline) and a weight-based amount of N6LS, as described in the IB. Preparation of N6LS (with and without rHuPH20) for SC administration will not require any diluent.

There are 6 different schedules in the study described in Appendix I.

7.2. N6LS (VRC-HIVMAB091-00-AB) Vialed Product

The N6LS product label designates the long-term storage temperature as -35°C to -15°C. Clinical site storage in a qualified, continuously monitored, temperature-controlled freezer with temperature excursions between -45°C to -10°C is acceptable.

Following thaw, N6LS vials may be stored for up to 24 hours at 15°C to 27°C and/or up to 4 weeks at 2°C to 8°C. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, vials must be equilibrated to 15°C to 27°C for a minimum of 60 minutes and may be held at this temperature for up to 8 hours prior to product preparation.

7.3. EDP Vialed Product

EDP is supplied as a sterile solution at a concentration of 1 mg/mL in 2 mL single-use glass vial containing 0.5 mg rHuPH20 (~110,000 U/mL). EDP should be stored as labeled, either at -20°C ± 5°C or 5°C ± 3°C and protected from light. Vials of EDP for injection can be removed from frozen storage and placed in the refrigerator at 2°C to 8°C for thawing (1 to 2 hours), or room temperature (20ºC to 25ºC) for 10 to 30 minutes. Once thawed, vials of EDP may be kept at room temperature (20ºC to 25ºC) for up to 24 hours before use and protected from bright light and direct sunlight.

7.4. Temperature Excursions

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

1. Quarantine the affected product in a separate area. If the excursion results in thawed material, it must not be refrozen. Thawed vials must be quarantined at 5°C ± 3°C.
2. Report the excursion to the IND sponsor's authorized representative (SAR) or designee, any other parties required by site procedures, and via email to VRCProductinquiries@nih.gov. 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.
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. Preparation of Study Product(s) (N6LS ± rHuPH20) for Administration

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

N6LS is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at 15°C to 27°C or storage at 2ºC to 8ºC.

The following instructions apply to thawing N6LS:

1. Thaw vial(s) for a minimum of 90 minutes at 15°C to 27°C after removing from the freezer. (DO NOT move vials directly from the freezer to storage at 2°C to 8°C.)
2. 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 7.2.
3. Prior to preparation for administration, vials should be swirled for 30 seconds with sufficient force to resuspend any visible particles, yet avoiding foaming. DO NOT SHAKE THE VIALS.
    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 dissolve or if 10 or fewer visible particles are present within the maximum storage times described in Section 7.2, the vials may be used for product preparation.

c. Refrigerated product must be equilibrated at 15°C to 27ºC for a minimum of 60 minutes before preparation and must be used within 8 hours of any subsequent return to 15°C to 27ºC.

4. If the thawed material is not administered within 24 hours of thaw, follow the storage information provided in Section 7.2.

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

7.5.1. N6LS: Preparation for IV Administration

For each IV infusion order, the subject's weight, dose level, and study group code will be included in the pharmacy order. To prepare an IV infusion, the pharmacist will: 1) fill an empty sterile bag with 100 mL of normal saline or (if commercially available) obtain a pre-filled 100 mL bag of normal saline, 2) calculate the total milligrams of N6LS needed, 3) retrieve the minimum number of thawed vials required to prepare the full dose, 4) withdraw the necessary amount of N6LS, 5) add this volume to the sterile bag using good pharmacy practices to maintain sterility, and 6) immediately remove all air remaining in the bag. Prepared IV bags should contain 10 particles or fewer to proceed with the administration to subjects.

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

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

7.5.2. N6LS: 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 N6LS vials needed to prepare the full dose. Prior to preparation for administration, vials should be gently swirled for 30 seconds avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, follow instructions in Section 7.5.

The needed volume of N6LS must be withdrawn from the vial into 1 to 4 syringes (BD Luer-Lok 3 mL syringe; REF # 309657) using a 5 micron filter needle (BD Blunt Fill Needle – Filter , 18G 1 ½ inch; REF# 305211). A new filter needle must be used for each syringe. The filter needle must be discarded prior to dispensing and replaced with a needle suitable for SC injection at the time of administration.

The product may be administered by direct SC injection with needle and syringe. The clinician will use proper SC technique to ensure administration into the SC fatty layer and a slow push to minimize discomfort or the excessive distention of overlying skin.

7.5.3. N6LS with rHuPH20: Preparation for SC Administration via Infusion Pump

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 of N6LS and units of rHuPH20 needed to achieve a 2000 U/mL concentration of rHuPH20, and retrieve the minimum number of thawed vials of N6LS and rHuPH20 needed to prepare the full dose (inclusive of infusion tubing residual volume). Prior to preparation for administration, vials of N6LS should be gently swirled for 30 seconds. AVOID FOAMING and DO NOT SHAKE THE VIALS. If particles are observed, follow instructions in Section 7.5. The vial(s) of EDP should be placed at room temperature (20°C to 25°C) for a minimum of 10 to 30 minutes (but for not more than 24 hours at 20°C to 25°C), and then gently swirled and inverted 3-5 times to mix thoroughly.

The required volume of N6LS must be withdrawn from the N6LS vial using a 5 micron filter needle (e.g., BD Blunt Fill Needle – Filter , 18G 1 ½ inch; REF# 305211) and gently injected into a new vial/recipient used for mixing. The required volume of EDP must be withdrawn from the EDP vial using a BD Luer-Lok 1 mL syringe and gently injected into the vial/recipient containing N6LS. The combined N6LS and EDP solution should then be mixed thoroughly by gentle swirling and inversion, 5 to 6 times (~10 seconds), while avoiding foaming. The mixed material can then be drawn into a sterile syringe with size dependent on total fill volume (*Note:* The prepared syringe should contain sufficient volume to accommodate the final dose volume, the priming volume, and the residual volume in the syringe after infusion.) The product may be administered in a single site using an infusion pump and syringe (i.e., Terumo Surflo® 23G winged infusion set with B/Braun extension set [product code ET06L or equivalent] and Medfusion syringe pump or equivalent) at a rate of 2-3 mL/min to ensure accurate and consistent administration. The clinician will use proper SC technique to ensure administration into SC fatty layer.

7.5.4. Handling of Prepared Product for IV or SC Administration: N6LS and N6LS+rHuPH20

After product preparation in an IV bag, the prepared N6LS may be stored at 15°C to 27°C for a maximum of 8 hours total, including the infusion time. Product may not be stored in direct sunlight.

After preparation in syringes for SC administration, the prepared N6LS may be stored at 2°C to 8°C for up to 24 hours, followed by storage at 15°C to 27°C for up to 4 hours, including administration time. The product may not be stored in direct sunlight.

Chemical and physical in-use stability data supports storage of N6LS mixed with EDP in syringes at 2°C to 8°C for up to 24 hours and at 15°C to 27°C for up to 4 hours, including administration time.

7.6. Labeling of Study Product

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

7.7. 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 all study products. Electronic documentation as well as paper copies may be used.

7.8. Study Product Disposition

Empty vials, including equipment used to prepare the N6LS and EDP mixture, and the unused portion of a vial will be discarded in a biohazard containment bag for incineration or decontamination by autoclave and disposed in accordance with the institutional or pharmacy policy. Partially used vials will not be administered to other subjects or used for *in vitro* experimental studies. Any unopened vials that remain at the end of the study will be returned to the production facility or discarded at the discretion of the sponsor in accordance with policies that apply to investigational agents.

8. HUMAN SUBJECT PROTECTIONS AND ETHICAL OBLIGATIONS

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

8.1. Informed Consent

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

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

The 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 will be provided to the subject.

8.2. Risk/Benefit Assessment

8.2.1. Potential Risks

Risks of N6LS and mAb Administration

Typically, the side effects of MAbs are mild but may include reactions at injection site (pain, redness, bruising, swelling), fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain. Up to Grade 3 injection site erythema has been observed after N6LS+ rHuPH20 injection, and some injection site reactions have lasted up to six weeks before completely resolving. 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.

Administration of MAbs may cause immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies. However, these reactions are rare and more often associated with MAb targeted to human proteins or with the use of murine monoclonal antibodies which would have a risk of human anti-mouse antibodies [33]. In this regard, as N6LS is expected to have a low risk of such side effects since it is directed against a viral antigen and is human in origin.

Published experience with other human MAb directed against the cell surface targets on lymphocytes have shown that infusion of a MAb may be associated with cytokine release, causing a reaction known as "cytokine release syndrome" (CRS) [34]. Most infusion-related events occur within the first 24 hours after beginning administration. Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension and hypoxia, are infrequent and more often associated with MAbs targeted to human proteins or when a non-human MAb, such as a murine MAb, is used [33]. Specifically, with regard to the rare CRS reactions, these generally

occur within the first few hours of beginning the infusion and are more common with the first MAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the MAb and the burden of target cells is greatest at the time of the first MAb treatment. With licensed therapeutic MAbs, CRS is managed by temporarily stopping the infusion, administration of histamine blockers and restarting the infusion at a slower rate [35].

Delayed allergic reactions to other MAbs may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the MAb and is noted to be more common with chimeric types of MAbs [33].

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

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

Risks of EDP Coadministration

EDP coadministration may cause mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection site reactions have occurred less frequently and include burning, erythema, pain, and numbness. Mild-to-moderate headache is also commonly reported. Adverse events in clinical trials have otherwise reflected the adverse reaction profiles of the co-administered drug or have been associated with the rapid introduction of a relatively large volume of fluid in the SC space.

Risks of Blood Drawing

Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. In this study, an IV line that can be used for the collection of blood may be left in place for several hours on the days when there are frequent PK blood draws. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site and rarely, infection, vein irritation (called phlebitis), or blood clot.

8.2.2. Benefits

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

8.3. Institutional Review Board

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

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

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

8.4. Subject Confidentiality

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

8.5. Plan for Use and Storage of Biological Samples

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

8.5.1. Use of Samples, Specimens and Data

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

Genetic testing may be performed in accordance with the genetic testing information that was included in the study Informed Consent Form (ICF).

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

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

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

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

8.5.2. Storage and Tracking of Blood Samples and Other Specimens

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

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

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

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

8.5.4. Loss or Destruction of Samples, Specimens or Data

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

8.6. Subject Identification and Enrollment of Study Subjects

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

8.7. Costs

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

8.8. Compensation

Subjects will be compensated for time and inconvenience in accordance with the standards for compensation of the Clinical Research Volunteer Program. Study product administration.

accompanied by the same day PK blood draws combined will be $430; product administration visits without PK blood draws will be $375. The compensation will be $200 for scheduled visits that include blood drawing, $85 for clinic visits that do not include a blood draw or procedure, and $25 total for timely completion of all 3 days of the electronic diary.

8.9. Safety Monitoring

Close cooperation between the designated members of the Protocol Team will occur to evaluate and respond to individual AEs in a timely manner. The VRC designated Safety Officer for the day conducts a daily safety review of clinical data per VRC Standard Operating Procedures. The PSRT, comprised of the PI, Associate Investigators, Study Coordinator, Protocol Specialists, other Study Clinicians, and MO will review the summary study safety data reports on a weekly basis through 4 weeks after the last subject receives the last product administration and will continue to monitor the safety data reports on a monthly basis through completion of the last study visit. A representative from Halozyme Therapeutics will also participate in any scheduled or *ad hoc* safety review meetings when Groups 7 and 8 are active.

8.10. 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. NIAID 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 LEGAL OBLIGATIONS

9.1. Protocol Amendments and Study Termination

Protocol amendments may be made only with the prior approval from the IND Sponsor. Agreement from the PI and MO must be obtained for all amendments to the protocol and the informed consent document. Approval from Halozyme Therapeutics, Inc. may also be required, in accordance with any cooperative research and development agreement (CRADA) or clinical trial agreement (CTA) established for the study. All study amendments will be submitted to the IRB for approval.

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

9.2. Study Documentation and Storage

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

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

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

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

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

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

9.3. Clinical Monitoring, Data Collection and Data Sharing

9.3.1. Clinical Monitoring Plan

The IND Sponsor or their authorized representatives are responsible for ensuring integrity of study data and compliance with the protocol. The PI will allow the study monitors, the IRB and the FDA to inspect study documents (e.g., consent forms, drug distribution forms, and case

report forms) and pertinent hospital or clinic records for confirmation of the study data. Site visits by study monitors will be made to monitor the following: study operations, quality of data collected in the research records, the accuracy and timeliness of data entered in the database, and to determine that all process and regulatory requirements are met. Study monitoring visits will occur as defined by the IND Sponsor approved monitoring plan.

9.3.2. Data Collection

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

9.3.3. Source Documents

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

9.3.4. Data Sharing

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

9.4. Language

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

9.5. Policy Regarding Research-Related Injuries

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

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APPENDIX I: SCHEDULE OF EVALUATIONS

Schedule 1: IV Group 1 (5 mg/kg), 3 (20 mg/kg), and 4 (40 mg/kg)																		
Visit Number		01R	02	02A	02B	02C	02D	03	04	06	07	08	09	10	11	15	16	17
Time After Infusion			Pre	EOI	1hr	3h	6h	24hr	48hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study		-42 to 0	D0	D0	D0	D0	D0	D1	D2	D7	D14	D21	D28	D56	D84	D112	D140	D168
Clinical	**Tube^**	**Screen**	**Enroll**	**Day of Administration**														
VRC 500 Screening Consent		X																
VRC 609 AoU; Consent			X															
[2] Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; also wt at visit 02		X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med history		X	X	X				X	X	X	X	X	X	X	X	X	X	X
[3]N6LS Administration				X														
Begin 3-day Diary Card				X														
CBC / differential	EDTA	3		3				3		3	3		3		3			
ALT, AST, ALP, creatinine	GLT	4		4				4		4	4		4		4			
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT	X		X							X				X			
[4]Pregnancy test: urine or serum		X	X	X							X					X		X
[4]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X							X					X		X
HIV Ab/Ag combo test	EDTA	3								3								
HIV risk-reduction counseling		X		X						X								
Research Samples																		
Timed PK samples	SST			4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
PBMCs	EDTA	20																
Serum	SST	8	8	8					8	8	8	8	8	8	8	8	8	8
Daily Volume (mL)		**38**	**8**	**19**	**4**	**4**	**4**	**4**	**11**	**12**	**22**	**19**	**12**	**19**	**12**	**19**	**12**	**12**	**12**
Cumulative Volume (mL)		**38**	**46**	**65**	**69**	**73**	**77**	**81**	**92**	**104**	**126**	**145**	**157**	**176**	**188**	**207**	**219**	**231**	**243**

Visit windows: Schedule visits 02A through 17 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, 15, 16 and 17 (±7 days).Visits 05, 12, 13 and 14 are not applicable to Schedule 1.

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

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

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

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

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

Schedule 2: SC Group 2 (5 mg/kg)																
Visit Number		01R	02	02A	03	04	05	06	07	08	09	10	11	15	16	17
Time After Infusion			Pre	EOI	24hr	48hr	72hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study		-42 to 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 609 AoU; Consent			X													
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; also wt at visit 02		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med history		X	X	X		X	X	X	X	X	X	X	X	X	X	X
[3] N6LS Administration				X												
Begin 3-day Diary Card				X												
CBC / differential	EDTA	3		3		3			3	3		3		3			
ALT, AST, ALP, creatinine	GLT	4		4		4			4	4		4		4			
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT	X		X						X				X			
[4]Pregnancy test: urine or serum		X	X	X						X					X		X
[4]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X						X					X		X
HIV Ab/Ag combo test	EDTA	3							3								
HIV risk-reduction counseling		X		X					X								
Research Samples																	
Timed PK samples	SST			4		4	4	4	4	4	4	4	4	4	4	4	4
PBMCs	EDTA	20															
Serum	SST	8	8	8			8	8	8	8	8	8	8	8	8	8	8
Daily Volume (mL)		**38**	**8**	**19**	**0**	**11**	**12**	**12**	**22**	**19**	**12**	**19**	**12**	**19**	**12**	**12**	**12**
Cumulative Volume (mL)		**38**	**46**	**65**	**65**	**76**	**88**	**100**	**122**	**141**	**153**	**171**	**184**	**203**	**215**	**227**	**239**

Visit windows: Schedule visits 02A through 17 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, 15, 16, 17 (±7 days). Visits 12-14 are not applicable to Schedule 2.

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

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

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

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

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

Schedule 3: SC Group 5 (5 mg/kg by repeat dosing)																							
Visit Number			01R	02	02A	03	04	05	06	07	09	10	11	11A	11E	12	13	14	15	16	17	17A	17E
Time After Infusion				Pre D0	EOI D0	24hr	48hr	72hr	1wk	Wk2	Wk4	Wk8	Pre Wk12	EOI Wk12	24hr	72hr	Wk13	Wk14	Wk16	Wk20	Pre Wk24	EOI Wk24	24hr
[1]Day of Study			-42 to 0	D0	D0	D1	D2	D3	D7	D14	D28	D56	D84	D84	D85	D87	D91	D98	D112	D140	D168	D168	D169
Clinical	**Tube^**	**Screen**	**Enroll**	**Day of injection**									**Day of injection**								**Day of injection**		
VRC 500 Screening Consent		X																					
VRC 609 AoU; Consent			X																				
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; wt at visits 02, 11, and 17		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Complete med history at screen; then interim med hx		X	X	X		X	X	X	X	X	X	X	X			X	X	X	X	X	X		
[3] N6LS Administration				X									X								X		
Begin 3-day Diary Card				X									X								X		
Phone contact; clinic visit if indicated															X								X
CBC / diff	EDTA	3		3		3			3	3		3	3			3	3	3		3	3		
ALT, AST, ALP, creatinine	GLT	4		4		4			4	4		4	4			4	4	4		4	4		
Total bili, BUN, albumin, protein, calcium Na, K, Cl, CO_2, glucose (CMP)	GLT	X		X						X			X					X			X		
[4]Pregnancy test: urine or serum		X	X	X						X			X					X			X		
[4]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X						X			X					X			X		
HIV Ab/Ag combo test	EDTA	3							3								3						
HIV risk-reduction counseling		X		X					X				X				X				X		
Research Samples																							
Timed PK samples	SST			4		4	4	4	4	4	4	4	4			4	4	4	4	4	4		
PBMCs	EDTA	20																					
Serum	SST	8	8	8			8	8	8	8	8	8	8				8	8	8	8	8		
Daily Volume (mL)		**38**	**8**	**19**	**0**	**11**	**12**	**12**	**22**	**19**	**12**	**19**	**19**	**0**	**0**	**11**	**22**	**19**	**12**	**19**	**19**	**0**	**0**
Cumulative Volume (mL)		**38**	**46**	**65**	**65**	**76**	**89**	**100**	**122**	**141**	**153**	**172**	**191**	**191**	**191**	**202**	**224**	**243**	**255**	**273**	**293**	**293**	**293**

Visit windows: Schedule visits 02A through 11 with respect to day 0. Schedule visits 11A through 17 with respect to visit 11. Visit A (+10 min); Visit E (+ 1 day); Visits 03, 04, 05, and 12 (± 6 hrs); Visits 06, 07, 13, and 14 (±2 days); Visits 09, 10, 11, 15, 16 and 17 (±7 days, with not less than 21 days between injections). Visits 08, 11B, 11C, 17B, and 17C are not applicable to Schedule 3.

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

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

[3] The PK blood draw "visits," defined by hours after an injection, are relative to the exact time of the end of injection (EOI). The exact start and end times of product administration and the time of PK blood draw(s) are recorded to ensure accurate PK analysis. Subjects will be observed for 4 hours after the first product administration, and at least 2 hours after the second and third product administrations.

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

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

- Subjects who have only received one product administration will follow Schedule 3 through Visit 10, and then move to Schedule 5.
- Subjects who have received two product administrations will follow Schedule 3 through Visit 16 and then move to Schedule 5.

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

Schedule 3 (continued): SC Group 5 (5 mg/kg by repeat dosing)										
Visit Number*		18	19	20	21	22	23	24	25	26
Time After Infusion		72hr	Wk25	Wk26	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
Day of Study		D171	D175	D182	D196	D224	D252	D280	D308	D336
Clinical	**Tube^**									
Targeted physical exam, BP, pulse, temp		X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med hx		X	X	X	X	X	X	X	X	X
CBC / diff	EDTA	3	3	3		3				
ALT, AST, ALP, creatinine	GLT	4	4	4		4				
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT			X						
[1]Pregnancy test: urine or serum				X			X			X
[1]Pregnancy prevention counseling / Reproductive Information Form				X			X			X
HIV Ab/Ag combo test	EDTA		3							
HIV risk-reduction counseling			X							
Research Samples										
Timed PK samples	SST	4	4	4	4	4	4	4	4	4
Serum	SST		8	8	8	8	8	8	8	8
Daily Volume (mL)		**11**	**22**	**19**	**12**	**19**	**12**	**12**	**12**	**12**
Cumulative Volume (mL)		**307**	**329**	**348**	**360**	**379**	**391**	**403**	**415**	**427**

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

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

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

- Subjects who have only received one product administration will follow Schedule 3 through Visit 10, and then move to Schedule 5.
- Subjects who have received two product administrations will follow Schedule 3 through Visit 16 and then move to Schedule 5.

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

Schedule 4: IV Group 6 (20 mg/kg by repeat dosing)																										
Visit Number			01R	02	02A	02B	02C	02D	03	04	06	07	09	10	11	11A	11B	11E	12	13	14	15	16	17	17A	17B
Time After Day 0 Infusion				Pre D0	EOI D0	1hr	3hr	6hr	24hr	48h	Wk1	Wk2	Wk4	Wk8	Pre Wk 12	EOI Wk 12	1hr	24hr	72hr	Wk13	Wk14	Wk16	Wk20	Pre Wk24	EOI Wk24	1hr
[1]Day of Study			-42 to 0	D0	D0	D0	D0	D0	D1	D2	D7	D14	D28	D56	D84	D84	D84	D85	D87	D91	D98	D112	D140	D168	D168	D168
Clinical	**Tube^**	**Screen**	**Enroll**	**Day of infusion**											**Day of infusion**									**Day of infusion**		
VRC 500 Screening Consent		X																								
VRC 609 AoU; Consent			X																							
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; also wt at visits 02, 11, 17		X	X	X	X				X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	
Complete med history at screen; then interim med hx		X	X	X					X	X	X	X	X	X	X				X	X	X	X	X	X		
[3] N6LS Administration				X											X									X		
Begin 3-day Diary Card				X											X									X		
Phone contact; clinic visit if indicated																		X								
CBC / diff	EDTA	3		3					3		3	3		3	3				3	3	3		3	3		
ALT, AST, ALP, creatinine	GLT	4		4					4		4	4		4	4				4	4	4		4	4		
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT	X		X								X			X						X			X		
[4]Pregnancy test: urine or serum		X	X	X								X			X						X			X		
[4]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X								X			X						X			X		
HIV Ab/Ag combo test	EDTA	3									3									3						
HIV risk-reduction counseling		X		X							X				X					X				X		
Research Samples																										
Timed PK samples	SST			4	4	4	4	4	4	4	4	4	4	4	4	4	4		4	4	4	4	4	4	4	4
PBMCs	EDTA	20																								
Serum	SST	8	8	8						8	8	8	8	8	8					8	8	8	8	8		
Daily Volume (mL)		**38**	**8**	**19**	**4**	**4**	**4**	**4**	**11**	**12**	**22**	**19**	**12**	**19**	**19**	**4**	**4**	**0**	**11**	**22**	**19**	**12**	**19**	**19**	**4**	**4**
Cumulative Volume (mL)		**38**	**46**	**65**	**69**	**73**	**77**	**81**	**92**	**104**	**126**	**145**	**157**	**176**	**195**	**199**	**203**	**203**	**214**	**236**	**255**	**267**	**286**	**305**	**309**	**313**

Visit windows: Schedule visits 02A through 11 with respect to Day 0. Schedule visits 11A through 17 with respect to Visit 11. Visits A (+10 min); Visits B and C (±10 min); Visit 02D (-2 hrs); Visit E (+1 day); Visits 03, and 04 (±6 hrs); Visits 06, 07, 13, and 14 (±2 days); Visit 12 (+2 days), Visits 09, 10, 11, 15, 16 and 17 (±7 days, with not less than 21 days between infusions). Visits 05 and 08 are not applicable to Schedule 4.

[1] Day 0=day of first product administration. Day 0 is preferably scheduled within 14 days after enrollment, but may be scheduled up to 42 days after enrollment to allow for the possibility of study pauses or scheduling difficulty with the approval of the PI. Day 0 evaluations prior to product administration are the baseline for assessing subsequent AEs.
[2] Screening includes physical exam with vital signs, height (ht) and weight (wt). At other visits, if medically indicated, a targeted exam is performed. Otherwise only blood pressure (BP), pulse, and temperature are required, except at Visits 02, 11, and 17 when the current weight is also obtained to use for ordering the study product, dosed based on "mg/kg."
[3] The PK blood draw "visits," defined by hours after an infusion, are relative to the exact time of the end of infusion. Exact start and end times of product administration and the time of PK blood draw(s) are recorded to ensure accurate PK analysis. All subjects will be observed for 4 hours after the first product administration, and at least 2 hours after the second and third product administrations.
[4] Pregnancy test results must be negative for women of reproductive potential before each product administration. Complete a Reproductive Information Form when pregnancy test given.

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

- Subjects who have only received one product administration will follow Schedule 4 through Visit 10, and then move to Schedule 5.
- Subjects who have received two product administrations will follow Schedule 4 through Visit 16 and then move to Schedule 5.

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

Schedule 4 (continued): IV Group 6 (20 mg/kg by repeat dosing)											
Visit Number*		17E	18	19	20	21	22	23	24	25	26
Time After Infusion		24hr	72hr	Wk25	Wk26	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
Day of Study		D169	D171	D175	D182	D196	D224	D252	D280	D308	D336
Clinical	**Tube^**										
Targeted physical exam, BP, pulse, temp			X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med hx			X	X	X	X	X	X	X	X	X
Phone contact; clinic visit if indicated		X									
CBC / diff	EDTA		3	3	3		3				
ALT, AST, ALP, creatinine	GLT		4	4	4		4				
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT				X						
[1]Pregnancy test: urine or serum					X			X			X
[1]Pregnancy prevention counseling / Reproductive Information Form					X			X			X
HIV Ab/Ag combo test	EDTA			3							
HIV risk-reduction counseling				X							
Research Samples											
Timed PK samples	SST		4	4	4	4	4	4	4	4	4
Serum	SST			8	8	8	8	8	8	8	8
Daily Volume (mL)		**0**	**11**	**18**	**19**	**12**	**19**	**12**	**12**	**12**	**12**
Cumulative Volume (mL)		**316**	**327**	**345**	**364**	**376**	**395**	**407**	**419**	**431**	**443**

Visit windows: Schedule visits 17A through 26 with respect to visit 17. Visit E (+1 day); Visit 18 (+2 days), Visits 19-22 (±2 days), and Visits 23-26 (±7 days).

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

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

- Subjects who have only received one product administration will follow Schedule 4 through Visit 10, and then move to Schedule 5.
- Subjects who have received two product administrations will follow Schedule 4 through Visit 16 and then move to Schedule 5.

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

Schedule 5: For Subjects in Groups 5 and 6 Discontinued from Further Product Administration(s)									
Visit Number			11	15	16	17	21	22	23
Time After Infusion			Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36
Day of Study			D84	D112	D120	D168	D196	D224	D252
Clinical		**Tube^**							
Targeted exam, BP, pulse, temp			X	X	X	X	X	X	X
Interim med history			X	X	X	X	X	X	X
Pregnancy test: urine or serum				X		X			X
Pregnancy prevention counseling/ Reproductive Information Form				X		X			X
Research Samples									
PK samples		SST	4	4	4	4	4	4	4
Serum		SST	8	8	8	8	8	8	8
Daily Volume (mL)			**12**	**12**	**12**	**12**	**12**	**12**	**12**
If starting at Visit 11	**Cumulative Volume (mL), Group 5**		**184**	**196**	**208**	**220**			
	Cumulative Volume (mL), Group 6		**188**	**200**	**212**	**224**			
If starting at Visit 17	**Cumulative Volume (mL), Group 5**					**285**	**297**	**309**	**321**
	Cumulative Volume (mL), Group 6					**298**	**310**	**322**	**334**

Visit windows: ±7 days for all visits shown.

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

- If only one product administration was received, subjects will follow their originally assigned study schedule through Visit 10 and then move to Schedule 5 for Visits 11-17. The final study visit will be Visit 17 for these subjects.
- If two product administration were received, subjects will follow their originally assigned study schedule through Visit 16 and then move to Schedule 5 for Visits 17-23. The final study visit will be Visit 23 for these subjects.

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

Schedule 6: N6LS + rHuPH20 SC Infusion Groups 7 (5 mg/kg) and 8 (20 mg/kg)																		
Visit Number			01R	02	02A	02B	03	04	05	06	07	08	09	10	11	15	16	17
Time After Infusion				Pre	EOI	4hr	24hr	48hr	72hr	Wk1	Wk2	Wk3	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24
[1]Day of Study			-42 to 0	D0	D0	D0	D1	D2	D3	D7	D14	D21	D28	D56	D84	D112	D140	D168
Clinical	**Tube^**	**Screen**	**Enroll**	**Day of Administration**														
VRC 500 Screening Consent		X																
VRC 609 AoU; Consent			X															
[2]Screen: Physical exam, ht, wt; Other: targeted exam, BP, pulse, temp; also wt at visit 02		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Complete med history at screen; then interim med history		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X
[3] N6LS Administration				X														
Begin 3-day Diary Card				X														
CBC / differential	EDTA	3		3			3			3	3		3		3			
ALT, AST, ALP, creatinine	GLT	4		4			4			4	4		4		4			
Total bili, BUN, albumin, protein, calcium, Na, K, Cl, CO_2, glucose (CMP)	GLT	X		X							X				X			
[4]Pregnancy test: urine or serum		X	X	X							X					X		X
[4]Pregnancy prevention counseling/ Reproductive Information Form		X	X	X							X					X		X
HIV Ab/Ag combo test	EDTA	3								3								
HIV risk-reduction counseling		X		X						X								
Research Samples																		
Timed PK samples	SST			4		4	4	4	4	4	4	4	4	4	4	4	4	4
Serum	SST	8	8	8				8	8	8	8	8	8	8	8	8	8	8
PBMC and Plasma	EDTA	20		10									10	10				
Daily Volume (mL)		**38**	**8**	**29**	**0**	**4**	**11**	**12**	**12**	**22**	**19**	**12**	**29**	**22**	**19**	**12**	**12**	**12**
Cumulative Volume (mL)		**38**	**46**	**75**	**75**	**79**	**90**	**102**	**114**	**136**	**155**	**167**	**196**	**218**	**237**	**249**	**261**	**273**

Visit windows: Schedule visits 02A through 17 with respect to day 0. Visit 02A (+10 min); Visit 02B (± 10 min); Visits 03, 04, 05 (± 6 hrs); Visits 06, 07, 08, 09 (±2 days); Visits 10, 11, 15, 16, 17 (±7 days). Visits 12-14 are not applicable to Schedule 6.

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

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

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

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

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

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

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

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

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

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

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

Table for Grading Severity of Adverse Events:

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

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

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

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

  Subclinical CMP results for sodium, potassium, chloride, bicarbonate, BUN, and glucose will not be considered an AE unless grade 2 or greater.

PRINCIPAL INVESTIGATOR: Richard Wu, MD

STUDY TITLE: VRC 609 (18I0105): A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB091-00-AB (N6LS), Administered Intravenously or Subcutaneously with or without Recombinant Human Hyaluronidase PH20 (rHuPH20) to Healthy Adults

STUDY SITE: NIH Clinical Center

Cohort: Healthy Volunteer

Consent Version: October 07, 2022, Version 9.0

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Richard Wu, MD., [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 N6LS. N6LS is a monoclonal antibody (mAb) that targets HIV. The main purpose of this study is to evaluate if N6LS is safe and how your body responds to it. Since this is the first time N6LS will be given to people, we do not know how your body will respond. We also want to check if your body will recognize N6LS and make an immune response to it. You cannot get HIV from N6LS.

About 32 to 40 people will take part in this study at the NIH Clinical Center in Bethesda, MD. Study groups 1-6 have completed the study. If you decide to take part, you will be enrolled in Groups 7 or 8 and you will be in the study for about 24 weeks (6 months) and get N6LS one time on Day 0 as an injection in the fat under your skin, subcutaneously (SC). N6LS will be mixed with rHuPH20. rHuPH20 helps to increase the distribution of injected drugs.

If you have side effects from N6LS, we expect them to like the side effects that occur with similar mAbs. These side effects usually occur within the first 24 hours or few days after the mAb is given and include local symptoms such as pain, redness, swelling, and itching, but injection site redness may take up to 6 weeks to fully resolve. 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 N6LS. N6LS has been used in the lab to block an HIV-like virus from causing infection in animals. The U.S. Food and Drug Administration (FDA) only allows it to be used for research because it is an experimental product. The study will also test N6LS mixed with an enzyme, rHuPH20 (recombinant human hyaluronidase PH20). rHuPH20 increases the spread of fluids injected underneath your skin (subcutaneously, SC) and allows for the rapid delivery of large volume injections that can be given with a single needle.

This study is the first time N6LS is tested in humans. N6LS is given into a vein in your arm (intravenously, IV) or as an injection underneath your skin subcutaneously. This study will be the first to test N6LS mixed with rHuPH20 in Groups 7 and 8. This study uses the same strength of enzyme that is given to patients receiving FDA approved products like trastuzumab and rituximab, used to treat cancer; and HyQvia®, used to treat immune problems in people with low antibody levels.

The goals of this study are:

- To see if N6LS alone and N6LS mixed with rHuPH20 is safe and well-tolerated.
- To measure the amount of N6LS that can be found in your body after you get it and how the levels of N6LS change over time.
- To check if your body will recognize N6LS and make a response to it.

You will need to complete about 13 to 26 clinic visits over 24 to 48 weeks depending on your study group.

STUDY PRODUCT(S)

The N6LS antibody is a monoclonal antibody (MAb) that targets HIV. Monoclonal means that all the N6LS antibodies are exactly the same and have been made artificially in the lab. The part of N6LS that binds to HIV was first discovered in a person who had HIV and controlled the infection for more than 15 years without taking any HIV medicine. Scientists at the NIH studied many antibodies this person made, and then figured out how to make them in the lab. They then made changes to the antibodies so that they can stay in the body longer than usual. N6LS was made in the same high standards that are required for medications normally prescribed to people.

We do not know if N6LS can be used to prevent or treat HIV in humans. This study will not be able to answer this question. Different studies will have to be done to do that.

You cannot get HIV from N6LS.

N6LS will be given together with rHuPH20 in study Groups 7 and 8. Your body naturally builds up and breaks down a substance called hyaluronan, which is a chain of natural sugars that are part of the normal tissue under your skin. rHuPH20 works by breaking down the hyaluronan. This way there is more space underneath your skin for larger amounts of N6LS to enter more easily. Once rHuPH20 is gone, your body builds the hyaluronan back up. The changes caused by rHuPH20 are gone within 24-48 hours after it is given.

WHAT WILL HAPPEN DURING THE STUDY?

The study will have 8 groups as shown in the Study Design table. Each group will have about 3 to 5 people in it. Different groups will get different doses of N6LS. Some groups will get more than one dose. Most people will get N6LS into a vein (IV). Some people will get N6LS with or without rHuPH20 into the belly fat under the skin (SC). You will be in the clinic for about 8 hours on the day(s) N6LS is given. Other clinic visits will take about 2 hours.

The study will last about 24 weeks for people in Groups 1-4, 7, and 8 because they will only get N6LS once. This will allow us to see if the doses of the antibody are safe and how long it lasts in the body.

The study will last for about 48 weeks for people in Groups 5 and 6 because they will get N6LS three times. This will allow us to see how much of the antibody stays in the body through three doses.

We also want to see the differences between getting N6LS by the IV or SC routes and the effect of N6LS mixed with rHuPH20 given in one SC injection. This information will be helpful for future uses of N6LS and rHuPH20.

Enrollment in Groups 1-6 is complete. If you agree to take part in this study, you will be enrolled in Group 7 or Group 8 and get 1 dose of N6LS + rHuPH20. You will be weighed on the day N6LS is to be given. Your body weight is used to calculate the amount of N6LS you will get.

The dose groups are shown in the Study Design table.

Study Design

Dose Groups	Participants	Study Products			Dosing Schedule			Total Number of Study Visits
		N6LS Dose	rHuPH20	Dosing Site	Day 0	Week 12	Week 24	
1	3	5 mg/kg	-	IV	X			13
2	3	5 mg/kg	-	SC	X			14
3	3	20 mg/kg	-	IV	X			13
4	3	40 mg/kg	-	IV	X			13
5	5	5 mg/kg	-	SC	X	X	X	25
6	5	20 mg/kg	-	IV	X	X	X	24
7	5	5 mg/kg	+	SC	X			14
8	5	20 mg/kg	+	SC	X			14
Total	**32**							

IV= using an arm vein; SC = under skin

Note: The dose of rHuPH20 is 2000 units per mL relative to the N6LS dose volume.

The study opened with the lowest dose of N6LS. The dose groups were spaced out to allow the study team to look over the safety data in each group. If there were no safety concerns in the lowest doses, then the next higher dose groups were enrolled. This pattern continued until all dose groups were enrolled.

A pregnancy test will be given to all woman who are able to become pregnant before N6LS is to be given. The result of the test must be negative in order to get N6LS.

- IV Dosing Groups (1, 3, 4, and 6):

  If you are assigned to Groups 1, 3, 4, or 6, a thin tube will be placed in your arm vein on the day you are to get the study product. We will place a second IV line in a vein on your other arm for blood sample collection. The N6LS will be given directly into your vein using a pump to control how fast it goes in. The goal is to give the N6LS in about 30 minutes, but may take longer. If you have side effects, the rate may be slowed down or stopped. When the infusion is done, we will monitor you in the clinic for 4 hours when you get N6LS the 1st time. We will collect blood samples at 1 and 3 hours after the infusion. You may be allowed to leave the clinic after 4 hours if there are no safety concerns, but must return for a blood draw at 6 hours after the infusion. You will also be asked to come back to the clinic 1 to 3 times during that first week after the infusion for sample collection.

  If you are in Group 6, you will get N6LS two more times during the study. We will monitor you in the clinic for at least 2 hours after you get the 2nd and 3rd infusions of N6LS. We will collect blood samples from you before and after each infusion. You will also be asked to come back to the clinic 4-5 times between and after these doses.

- SC Dosing Groups (2 and 5):

  If you are assigned to Groups 2 or 5, we will use a small needle to inject N6LS into the fatty tissue of your belly. We may use your arm or thigh area instead. You will get 1 to 4 of these injections for each dose. We will monitor you for 4 hours after you get N6LS the 1st time. If there are no safety concerns, you will be allowed to leave the clinic after the 4 hour safety check. If you are in Group 5, you will get N6LS two more times during the study. We will monitor you in the clinic for at least 2 hours after you get the 2nd and 3rd doses of N6LS. We will collect blood samples from you before the injection and then at every scheduled follow-up visit.

- SC Dosing Groups with rHuPH20 (7 and 8):

  If you are assigned to Groups 7 or 8, we will use a small needle attached to a pump to infuse the mix of N6LS and rHuPH20 into the fatty tissue of your belly. We will monitor you for 4 hours after you get N6LS. If there are no safety concerns, you will be allowed to leave the clinic after the 4-hour safety check. We will collect 6 tubes of blood from you before the infusion, 1 tube 4 hours after the infusion, and then 2-5 tubes of blood at each follow-up visit.

We will give you a measuring tool and thermometer and ask you to check your temperature every day for 3 days after you get the study product(s). You will need to record your highest temperature and any symptoms you have. You will use the 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 a computer, you may use a paper diary instead.

You should tell a VRC nurse or doctor as soon as possible if you have any side effects after you get the study product(s). You can reach the staff by phone 24 hours a day, seven days a week. If you have symptoms, you may 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: We will check you for any health changes or problems at each visit. We will ask you how you are feeling and if you have taken any medications. We will draw about 1 to 5 tubes of blood at scheduled study visits. We will tell you right away if any of your test results show a health problem.

We will use some blood samples to study if your body develops an immune response to N6LS. These tests are for research purposes only and are not for checking on your health. We will not give you these results. After completing this study, we may invite you to take part in another study for follow-up sample collection.

Clinical studies follow a set schedule. This helps us to answer the research questions. The visit schedule is a little flexible, but it is important that you work with the staff to follow the schedule as closely as possible. You should try to not miss any visits.

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 N6LS. 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

A group of physicians and scientists at NIH will monitor safety in this study. This group will review the information from the study and will pay close attention to possible harmful reactions. If serious side effects occur, further dosing with the study product(s) may be delayed or canceled.

GENETIC TESTING

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

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

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Thirty-two (32) to 40 people will take part in this study at the NIH Clinical Center in Bethesda, Maryland.

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

Risks of N6LS: This study is the first time N6LS is given to people. As of August 4, 2021, N6LS has been given to 14 people by IV and 12 people by SC injection.

The safety data described below is taken from studies with other antibodies that are like N6LS and may work the same and from observations seen in the study so far. Most side effects tend to happen within the first 24 hours to a few days after product administration.

Side effects to N6LS-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 N6LS at a controlled rate. If you develop symptoms while N6LS is being given, then tell the nurse right away. Slowing or stopping the flow rate may help improve the symptoms.

Side effects to N6LS-like antibodies given by SC dosing may include pain/tenderness, itchiness, redness and/or swelling at the site of injection. Two people in the trial who received N6LS +rHuPH20 SC developed larger injection site redness. The redness was almost 8 inches at its largest and took up to 30 days to go away. They did not have other signs or symptoms such as fever, scarring, or any other skin related issues. The team determined it was safe to continue

because both individuals tolerated the redness well and did not have abnormal laboratory tests. Therefore the redness was judged not to represent an increased safety risk for study participants. Tiredness, muscle pain outside the injection site, and headache have also been reported. These symptoms usually cleared 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. N6LS is not expected to increase the risk of serious infections because it attacks a virus and does not target the human immune system.

Unknown risks: N6LS may have other side effects that are not yet known. Participation in this study may affect your eligibility for future monoclonal antibody studies. We will give you any new information about risks or other information that may affect your decision to continue in the study as it becomes available.

You may not donate blood while taking part in this study and you may not donate blood for one year after the date of your last dose of N6LS.

Risks of rHuPH20: This study is the first time that a combination of N6LS and rHuPH20 will be given to people. The active ingredient in rHuPH20 (hyaluronidase) has been given to roughly 1,592 people alone and in combination with other products in controlled clinical studies by its manufacturer as of November 15, 2020. Also, SC injections of hyaluronidase when given with other antibodies and proteins, including 5 FDA-approved products, have been well-tolerated in over 600,000 people. Some people have experienced mild, short-term redness, pain, bruising, itching, swelling, tingling, numbness, and rash at the injection site. A few people have experienced more severe burning, redness, pain, and numbness, but this is less common. Several people have experienced mild to moderate headache.

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

Risks of Blood Drawing: Blood drawing may cause pain, bruising, and may cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. An IV line may be placed in your vein for a few hours on a day N6LS is given by IV. Problems at the IV site are usually mild and may include pain, bruising, minor swelling, or bleeding. Rarely, there may be an infection, vein irritation, nerve problem, or blood clot.

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to the fetus or

unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails while you are in the study. If you think or know you have become pregnant while participating in this research study, please contact the study team as soon as possible. If you get pregnant, you will not receive any further doses of N6LS, and we will not collect any more blood for research. However, you will be asked to continue with study follow-up visits to check on your health and to report the outcome of the pregnancy. If you plan to become pregnant in the future, please discuss with the study team how long you need to wait before becoming pregnant after completing the study.

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?

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 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 a steroid 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 similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

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.

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.

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?

You will be compensated for your time and inconvenience. Total compensation for completion of the study will be between $2500 to $4900 and is based on the number and type of study visits you complete. You will get:

- $200 for scheduled visits with a blood draw.
- $85 for clinic visits that do not include a blood draw.
- $430 for IV product administration visit(s) with blood draws on the same day.
- $430 for SC product administration visit(s) with blood draws on the same day.
- $375 for SC product administration visit(s) with no blood draw.
- $25 total for timely completion of all 3 days of an electronic diary.

You will get your compensation about 2 weeks after each completed visit by direct deposit into a bank account that you specify to the Volunteer Payment Office. If you are unable to finish the study, you will receive compensation for the parts you completed. Your compensation may need to be reported to the internal revenue service (IRS) as taxable income. IRS "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 payment. 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 payment. If you have unpaid debt to the federal government, some or all of your compensation may be automatically reduced to repay your debt.

REIMBURSEMENT

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

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

The NIH and the research team for this study have developed N6LS 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 N6LS.

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, NIAID or their agent(s)
- Qualified representatives from Halozyme Therapeutics, the pharmaceutical company who produces rHuPH20.

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, [redacted] nother researcher you may call is: [redacted] You may also call the NIH Clinical Center Patient Representative at [redacted] or the NIH Office of IRB Operations, at [redacted] 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: _____.

PRINCIPAL INVESTIGATOR: Richard Wu; VRC, NIAID

STUDY TITLE: VRC 609: A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB091-00-AB (N6LS), Administered Intravenously or Subcutaneously with or Without Recombinant Human Hyaluronidase PH20 (rHUPH20) to Healthy Adults

STUDY SITE: NIH Clinical Center

Cohort: *Healthy volunteer supplemental*

Supplementary Consent Version: *October 07, 2022, Version 8.0*

WHO DO YOU CONTACT ABOUT THIS STUDY?

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

Study Coordinator: [redacted]

Supplementary consent for extended genetic testing (optional)

You agreed to participate in VRC 609 study for testing of and an investigational human monoclonal antibody to the HIV-1 envelope. This additional consent covers optional extended genetic testing that you may agree to. You do not need to provide an additional sample if you agreed to extended genetic testing. If you do not agree to this additional testing, you still can participate in the VRC 609 study.

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

Genetic Data Sharing

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

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] Another researcher you may call is [redacted] You may also call the NIH Clinical Center Patient Representative at [redacted]

[redacted] or the NIH Office of IRB Operations at [redacted] 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 to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process with a non-English speaking subject and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:

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: _____.