PROTOCOL

HVTN 143/HPTN 109

A phase 1 clinical trial to evaluate the safety, tolerability, and pharmacokinetics of monoclonal antibodies VRC01.23LS, PGT121.414.LS and PGDM1400LS administered via intravenous infusion in adults without HIV

DAIDS DOCUMENT ID 39015

CLINICAL TRIAL SPONSORED BY

Division of AIDS (DAIDS)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)
Bethesda, Maryland, USA

STUDY PRODUCT(S) PROVIDED BY

DAIDS, NIAID, NIH, DHHS
(Bethesda, Maryland, USA)

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS
(Bethesda, Maryland, USA)

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Contents

1 Overview

Title

A phase 1 clinical trial to evaluate the safety, tolerability, and pharmacokinetics of monoclonal antibodies VRC01.23LS, PGT121.414.LS and PGDM1400LS administered via intravenous infusion in adults without HIV

Primary objective(s)

- To evaluate the safety and tolerability of VRC01.23LS when administered alone via intravenous (IV) route (Part A) and of VRC01.23LS + PGT121.414.LS + PGDM1400LS, when administered consecutively via IV route (Part B)

- To evaluate the serum concentrations and pharmacokinetics (PK) of VRC01.23LS when administered alone via IV (Part A) and of VRC01.23LS + PGT121.414.LS + PGDM1400LS, after consecutive administration via IV route (Part B)

- To evaluate the individual mAb-specific serum neutralizing activity of VRC01.23LS when administered alone via IV (Part A) and of VRC01.23LS + PGT121.414.LS + PGDM1400LS, after consecutive administration via IV route (Part B)

Study products

- **VRC-HIVMAB0115-00-AB (VRC01.23LS):** is a human mAb that targets the HIV-1 CD4 binding site (CD4bs). It was developed by the Vaccine Research Program (VRP)/ National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) and manufactured under current Good Manufacturing Practice (cGMP) standards at the Dale and Betty Bumpers Vaccine Research Center (VRC) Pilot Plant operated under contract by the VRC, Leidos Biomedical Research, Inc., Frederick, MD. Product is provided at 100 ± 10 mg/mL as 10 mL glass vials with a 6.25 ± 0.1 mL fill volume..

- **PGT121.414.LS:** is a human mAb that targets the HIV-1 V3 glycan, centered on N332. It is a derivative of PGT121 that was engineered for improved manufacturing, stability and in vivo elimination half-life by Just Biotherapeutics in collaboration with Dan Barouch and Collaboration for AIDS Vaccine Discovery (CAVD) investigators. The drug substance was manufactured under cGMP standards at Just-Evotec Biologics (Seattle, Washington) under contract to the Division of AIDS's (DAIDS) Vaccine Translational Research Branch (VTRB). The drug product was filled and released at the VRC Pilot Plant, operated under contract by VCMP, Leidos

Biomedical Research, Inc., Frederick, MD. Product is provided at 100 mg/mL as 10 mL glass vials with a 4.75 mL fill volume.

- **PGDM1400LS**: a human mAb that targets the HIV-1 V2 glycan, centered on N160. It is a derivative of PGDM1400 that was engineered to improve in vivo elimination half-life. It has been developed by the VRP of NIAID. PGDM1400LS was manufactured under cGMP standards at Just-Evotec Biologics (Seattle, Washington) under contract to DAIDS's VTRB. The drug product was filled and released at the VRC Pilot Plant, operated under contract by VCMP, Leidos Biomedical Research, Inc., Frederick, MD. The drug product is provided at 100 mg/mL as 10-mL glass vials with a 4.75-mL fill volume.

Table 1-1 Schema

Group	N	Antibody (Ab)	Dose/Route	M0	M6
Part A					
1	5*	VRC01.23LS	5 mg/kg IV	✓	
2[1]	5*	VRC01.23LS	20 mg/kg IV	✓	
3[1]	5*	VRC01.23LS	40 mg/kg IV	✓	
Part B[2]					
4	8	VRC01.23LS + PGT121.414.LS + PGDM1400LS	5 + 5 + 5 mg/kg IV	✓	✓
5	8	VRC01.23LS + PGT121.414.LS + PGDM1400LS	20 + 5 +5 mg/kg IV	✓	✓
6	8	VRC01.23LS + PGT121.414.LS + PGDM1400LS	20 + 20 + 20 mg/kg IV	✓	✓
7	8	VRC01.23LS + PGT121.414.LS + PGDM1400LS	40 + 5 + 5 mg/kg IV	✓	✓
8	30	VRC01.23LS + PGT121.414.LS + PGDM1400LS	40 + 40 + 40 mg/kg IV	✓	✓
Total	77				

IV = intravenous infusion

* Additional participants may be enrolled to ensure the availability of safety data from at least 5 participants in each group

[1] In Part A, opening enrollment in Group 2 follows review of safety data for participants in Group 1, enrollment in Group 3 follows review of safety data for participants in Group 2. Details are described in Section 11.3.1.

[2] Opening enrollment in Part B follows review of safety data for participants in Part A. All groups in Part B will enroll simultaneously, without restrictions.

Participants

About 77 adult volunteers without HIV aged 18 through 50 years in the Republic of South Africa

Design

Multicenter, randomized, open-label study

Duration per participant

6 months per participant in Part A and 12 months per participant in Part B of scheduled clinic visits

Estimated total study duration

22 months (includes enrollment, planned safety holds, and follow-up)

Investigational New Drug (IND) sponsor

DAIDS, NIAID, NIH, Department of Health and Human Services (DHHS) (Bethesda, Maryland, USA)

Study-product providers

- **VRC01.23LS:** VRC, NIAID, NIH, DHHS (Bethesda, Maryland, USA)
- **PGT121.414.LS:** DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)
- **PGDM1400LS:** DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)

HIV Vaccine Trials Network (HVTN) Leadership and Operations Center (LOC)

HIV Vaccine Trials Network (HVTN) Leadership Group/Core Operations Center, Fred Hutchinson Cancer Center (Fred Hutch) (Seattle, Washington, USA)

HIV Prevention Trials Network (HPTN) Leadership and Operations Center (LOC)

HIV Prevention Trials Network (HPTN), FHI 360, (Durham, North Carolina, USA)

HVTN Statistical and Data Management Center (SDMC)

Statistical Center for HIV/AIDS Research and Prevention (SCHARP), Fred Hutch (Seattle, Washington, USA)

HVTN Laboratory Center (LC)

HIV diagnostic laboratory

University of Washington Virology Specialty Laboratory (UW-VSL) (Seattle, Washington, USA)

Endpoint assay laboratories

- Duke University Medical Center (Durham, North Carolina, USA)
- South Africa Immunology Laboratory and National Institute for Communicable Diseases (Johannesburg, South Africa)
- Dartmouth College (Hanover, New Hampshire, USA)

Study sites

HVTN and HPTN Clinical Research Sites (CRSs) in the Republic of South Africa to be specified in the Site Announcement Memo

Safety monitoring

HVTN 143/HPTN 109 Protocol Safety Review Team (PSRT); HVTN Safety Monitoring Board (SMB)

1.1 Protocol Team

Protocol leadership

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HVTN Community engagement unit representative	Gail Broder Luciana Kamel Patricia Segura Kagisho Baepanye HVTN LOC, Fred Hutch	*HPTN Community program managers*	Jonathan Lucas Michelle Haber HPTN LOC, FHI 360
DAIDS VTRB representative	Mike Pensiero	*Community educators/recruiters*	Amelia Mfiki Groote Schuur CRS
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2 Ethical considerations

It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of clinical trials. The HVTN and HPTN (hereafter referred to as the "Networks") have addressed ethical concerns in the following ways:

- Network trials are designed and conducted to enhance the knowledge base necessary to find new methods for the prevention of HIV acquisition, using methods that are scientifically rigorous and valid, and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and/or other Good Clinical Practice (GCP) guidelines.

- Network scientists and operational staff incorporate the philosophies underlying major codes (1-3), declarations, and other guidance documents relevant to human subjects research into the design and conduct of HIV vaccine and prevention clinical trials.

- Network scientists and operational staff are committed to substantive community input—into the planning, conduct, and follow-up of its research—to help ensure that locally appropriate cultural and linguistic needs of study populations are met. Community Advisory Boards (CAB) are required by DAIDS and supported at all Network research sites to ensure community input, in accordance with Good Participatory Practices (GPP) and all local and national guidelines.

- Network clinical trial staff counsel study participants routinely on how to reduce their likelihood of acquiring HIV. Participants who acquire HIV during the trial are provided counseling on notifying their partners and about HIV acquisition according to local guidelines. Staff members will also counsel them about reducing their likelihood of transmitting HIV to others.

- The Networks require that all sites develop plans for the care and treatment of participants who acquire HIV during a trial. Each plan may be developed in consultation with representatives of host countries, communities from which potential trial participants will be drawn, sponsors, and the Networks. Participants who acquire HIV during the trial are referred to medical practitioners to manage their HIV and to identify potential clinical trials they may want to join. If a program for antiretroviral (ARV) therapy (ART) provision is not available at a CRS and ART is needed, a privately established fund will be used to pay for access to treatment to the fullest extent possible.

- The Networks provide training so that all participating sites similarly ensure fair participant selection, protect the privacy of research participants, and obtain meaningful informed consent. During the study, participants will have

their wellbeing monitored, and to the fullest extent possible, their privacy protected. Participants may withdraw from the study at any time.

- Prior to implementation, Network trials are rigorously reviewed by scientists who are not involved in the conduct of the trials under consideration.

- Network trials are reviewed by local and national regulatory bodies and are conducted in compliance with all applicable national and local regulations.

- The Networks design their research to minimize risk and maximize benefit to both study participants and their local communities. For example, Network protocols provide enhancement of participants' knowledge of HIV and HIV prevention, as well as counseling, guidance, and assistance with any social impacts that may result from research participation. Network protocols also include careful medical review of each research participant's health conditions and reactions to study products while in the study.

- Network research aims to benefit local communities by directly addressing the health and HIV prevention needs of those communities and by strengthening the capacity of the communities through training, support, shared knowledge, and equipment. Researchers involved in Network trials are able to conduct other critical research in their local research settings.

- The Networks value the role of in-country Institutional Review Boards (IRBs), Ethics Committees (ECs), and other Regulatory Entities (REs) as custodians responsible for ensuring the ethical conduct of research in each setting.

3 IRB/EC review considerations

US Food and Drug Administration (FDA) and other US federal regulations require IRBs/ECs/REs to ensure that certain requirements are satisfied on initial and continuing review of research (Title 45, Code of Federal Regulations [CFR], Part 46.111[a] 1-7; 21 CFR 56.111[a] 1-7). The following section highlights how this protocol addresses each of these research requirements. Each Network Investigator welcomes IRB/EC/RE questions or concerns regarding these research requirements.

This trial is being conducted in countries outside of the US, with funding from the US NIH among others. Due to this, the trial is subject to both US and local regulations and guidelines on the protection of human research subjects and ethical research conduct. Where there is a conflict in regulations or guidelines, the regulation or guideline providing the maximum protection of human research subjects will be followed.

In compliance with international and local (as appropriate) ICH and/or other GCP guidelines, each research location has a locally-based Principal Investigator (PI) who is qualified to conduct (and supervise the conduct of) the research; and the research addresses an important local health need for an HIV prevention method. In addition, the investigators take responsibility for the conduct of the study and the control of the study products, including obtaining all appropriate regulatory and ethical reviews of the research.

3.1 Minimized risks to participants

45 CFR 46.111 (a) 1 and 21 CFR 56.111 (a) 1: Risks to subjects are minimized.

This protocol minimizes risks to participants by (a) correctly and promptly informing participants about risks so that they can join in partnership with the researcher in recognizing and reporting harms; (b) respecting local/national blood draw limits; (c) performing direct observation of participants post–study-product administration and collecting information regarding side effects for several days post–study-product administration; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, study product administrations, HIV testing and counseling and HIV risk-reduction counseling; (e) providing HIV risk-reduction counseling and checking on contraception use (for persons assigned female sex at birth [AFAB] or intersex at birth and are capable of becoming pregnant; and (f) providing safety monitoring.

3.2 Reasonable risk/benefit balance

45 CFR 46.111(a) 2 and 21 CFR 56.111(a) 2: Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

In all public health research, the risk-benefit ratio may be difficult to assess because the benefits to a participant in overall good health are not as apparent as they would be in treatment protocols, where a study participant may be ill and may have exhausted all conventional treatment options. However, this protocol is designed to minimize the risks to participants while maximizing the potential value of the knowledge it is designed to generate.

3.3 Equitable participant selection

45 CFR 46.111 (a) 3 and 21 CFR 56.111 (a) 3: Subject selection is equitable

This protocol has specific inclusion and exclusion criteria for investigators to follow in admitting participants into the protocol. Participants are selected because of these criteria and not because of positions of vulnerability or privilege. Investigators are required to maintain screening and enrollment logs to document volunteers who screened into and out of the protocol and for what reasons.

3.4 Appropriate informed consent

45 CFR 46.111 (a) 4 and 5 and 21 CFR 56.111 (a) 4 and 5: Informed consent is sought from each prospective subject or the subject's legally authorized representative as required by 45 CFR 46.116 and 21 CFR Part 50; informed consent is appropriately documented as required by 45 CFR 46.117 and 21 CFR 50.27

The protocol specifies that informed consent must be obtained before any study procedures are initiated and assessed throughout the trial (see Section 9.1). Each CRS is provided training in informed consent by the Networks and is required to have a Standard Operating Procedure (SOP) on the informed consent process. The Networks require a signed consent document for documentation, in addition to chart notes or a consent checklist.

3.5 Adequate safety monitoring

45 CFR 46.111 (a) 6 and 21 CFR 56.111 (a) 6: There is adequate provision for monitoring the data collected to ensure the safety of subjects.

This protocol has extensive safety monitoring in place (see Section 11). Safety is monitored daily by HVTN clinical staff and routinely by the PSRT. In addition, the SMB periodically reviews study data.

3.6 Protect privacy/confidentiality

45 CFR 46.111 (a) 7 and 21 CFR 56.111 (a) 7: There are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

Privacy refers to an individual's right to be free from unauthorized or unreasonable intrusion into their private life and the right to control access to individually identifiable information about them. The term "privacy" concerns research participants or potential research participants as individuals whereas the term "confidentiality" is used to refer to the treatment of information about those individuals. This protocol respects the privacy of participants by informing them about who will have access to their personal information and study data (see Appendix A and Appendix B). The privacy of participants is protected by assigning unique identifiers in place of the participant's name on study data and specimens. In addition, each staff member at each study CRS in this protocol signs an Agreement on Confidentiality and Use of Data and Specimens with the Networks. In some cases, a comparable confidentiality agreement process may be acceptable. Each study CRS participating in the protocol is required to have an SOP on how the staff members will protect the confidentiality of study participants.

4 Background

4.1 Rationale for trial concept

In 2021 more than 38.4 million people were living with HIV, of which 1.5 million were newly diagnosed; and among these, only 28.7 million people were accessing ART (4). The use of ARVs for daily oral pre-exposure prophylaxis (PrEP) has been shown to be highly efficacious for HIV prevention across multiple populations, however global uptake has been suboptimal and the number of PrEP users with continued use of PrEP over time has been relatively low compared to the number of new HIV diagnoses (5, 6). It is clear that multiple strategies will be required to end the HIV epidemic, both in the US and globally, and that novel efforts to prevent, treat, and cure HIV are critically needed. One such alternative to daily oral PrEP is passive immunization with the use of broadly neutralizing antibodies (bnAbs), a promising approach that could contribute to a reduction of HIV incidence at a population level (7-9).

The discovery of multiple potent and bnAbs against HIV has led to the re-emergence of the concept that passive administration of antibodies (Abs) may be useful for prevention (10). These HIV-specific Abs that target the HIV envelope (Env) can prevent simian-human immunodeficiency virus (SHIV) in nonhuman primate (NHP) models and have been shown to reduce HIV RNA levels in people living with HIV (11-25). Until recently, these Abs were few in number, only targeting a narrow spectrum of HIV strains and Env epitopes. They are also noted to have inadequate potency when used in isolation; however, evidence suggests the use of combinations of bnAbs may result in better outcomes (26).

In the last decade, the increased interest in bnAbs has led to advancements in high throughput single-cell polymerase chain reaction (PCR) amplification and novel soluble Env baits resulting in isolation of new monoclonal antibodies (mAbs) with extraordinary potency and breadth (10, 27, 28). Once isolated, Ab engineering has allowed further enhancements in bnAbs' potency, half-life, solubility, stability, and manufacturability. These modifications expand their potential as preventative, therapeutic, and curative agents (29-34). The exploration of these bnAbs may be beneficial for future HIV prevention and therapeutic strategies when administered passively and warrant further research efforts (10, 35, 36).

Improved outcomes in Ab-mediated HIV-1 prevention efficacy are likely to be found with combinations of potent bnAbs, as innate resistance and selection of resistant isolates over time mitigate the effect of VRC01 (or likely any single bnAb), similar to observations with first-generation ART. The double or triple coverage afforded by a bnAb combination may limit early viral escape and reduce levels of incomplete neutralization.

This study is part of a series of studies that aim to evaluate safety and tolerability of bnAbs and whether combining bnAbs that target different sites on the virus is

additive or synergistic with respect to neutralization breadth and potency. These data will be critical for designing future bnAb studies. The potential of bnAbs in passive immunization and for future vaccine development for HIV prevention is enormous. This implementation should be complementary to existing modalities, such as ART, preexposure, and postexposure prophylaxis (7).

4.1.1 Combination bnAbs

Combinations of bnAbs targeting the CD4bs, V2 region, and V3 glycan region are thought to be among the most promising bnAb combinations to optimize both breadth and potency (27).

One example of this combination of bnAbs is VRC01 and its derivatives (LS, 07.523LS, and 01.23LS), which bind the CD4bs; PGDM1400 and its derivatives (LS), which bind the V2 region; and PGT121 and its derivatives (414.LS), which bind the V3 glycan region of the HIV Env glycoprotein. While VRC01.23LS is exceptionally broad, its HIV prevention efficacy is bolstered by the more potent, albeit less broad, complementary coverage of PGDM1400LS and PGT121.414.LS (see Figure 4-1 and Figure 4-2).

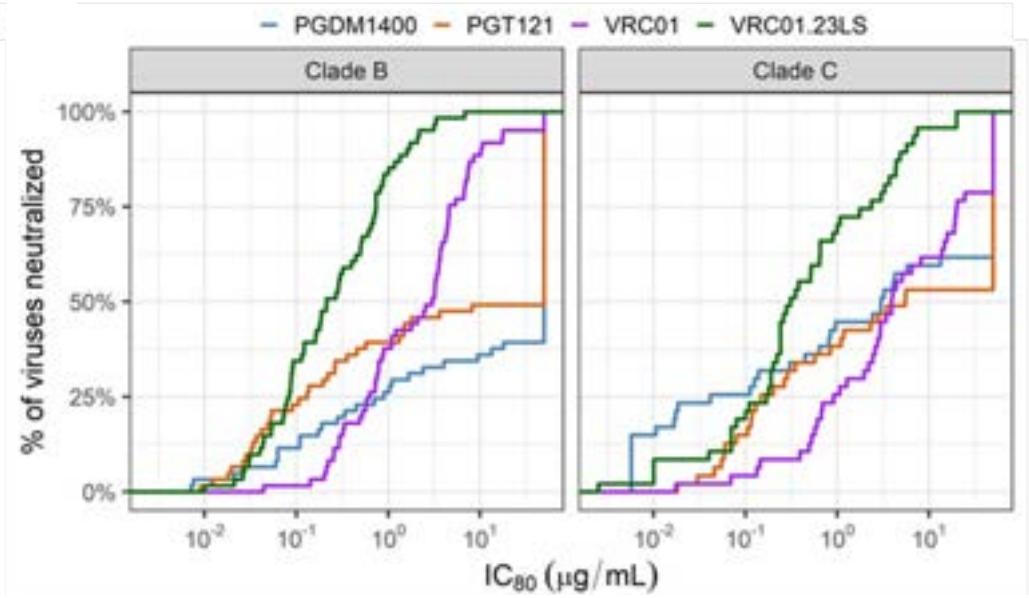

Figure 4-1 Breadth and potency curves for PGT121, PGDM1400, VRC01 and VRC01.23LS to the same panel of viruses.

Several clinical trials are evaluating combinations of VRC07-523LS, PGDM1400LS, and PGT121.414.LS and/or derivatives of these bnAbs among adults without HIV and in overall good health. The “parental” triple combination (VRC07-523LS + PGDM1400 + PGT121) was evaluated in the HVTN 130/HPTN 089 trial; the engineered PGT121.414.LS Ab alone and in combination with VRC07.523LS is being evaluated in the ongoing HVTN 136/HPTN 092 trial; and PGDM1400LS and the LS triple combination (VRC07-523LS + PGDM1400LS + PGT121.414.LS) is being evaluated in HVTN 140/HPTN 101. Data from HVTN 130/HPTN 089 suggest neither synergy nor

antagonism of PK or neutralization with the triple bnAb combination. These bnAbs alone and in combination have been safe and well tolerated in these studies.

Modeling informed by NHP analyses, and data from the HVTN 703/HPTN 081 trial (antibody-mediated prevention [AMP] study) which evaluated VRC01 alone to protect against HIV-1 acquisition (Figure 4-6), suggest that high doses of the LS triple combination will be necessary to achieve the ID80 ≥ 200 which was determined from results of the VRC01 AMP trial to be required for prevention of HIV-1 infection for approximately 6 months after each administration. (37). However, these doses (and the associated volumes required to administer them) could be significantly reduced with more potent versions of these Abs.

Indeed, enhanced versions of the promising CD4bs + V2+ V3 bnAb combination are in late preclinical development for clinical testing. Modeling from re-engineered versions of parental CD4bs + V2 + V3 bnAb combinations are shown in Figure 4-2 and Figure 4-3. The 80% inhibitory concentration (IC80) data for a panel of 108 viruses (61 from clade B and 47 from clade C) in the control groups of the AMP trials demonstrate increased neutralization, breadth, and potency when VRC01.23LS is used alone and in combination, when compared to the parental version (VRC01) alone or in combination with + PGT121 + PGDM1400 (Figure 4-2). Through advances in B-cell immunology, cloning, and structure-guided optimization techniques, numerous HIV-1 neutralizing mAbs were isolated and subsequently engineered to have potency and breadth greater than those of earlier antibodies. VRC07-523LS was found to be 5- to 8- fold more potent than VRC01, with an IC50 < 50 mcg/mL against 96% of HIV-1 pseudoviruses representing the major circulating HIV-1 clades, and an IC50 < 1 mcg/mL against 92% of HIV-1 viruses tested (15). VRC01.23 was found to be more potent than VRC07.523LS and to have a more favorable PK profile in FcRn transgenic mice.

HVTN 140/HPTN 101 takes advantage of the enhanced potency of VRC07 compared to VRC01 and combines VRC07-523LS with PGT121.414.LS and PGDM1400LS. Following this design, one of the aims of HVTN 143/109 is to assess half-life and PK of VRC01.23LS in comparison to its parental form. Additionally, the ease of cell line manufacturing makes VRC01.23LS a potentially useful candidate for future bnAb combination studies.

This proposed study of VRC01.23LS is a phase 1, dose-escalation, open-label clinical trial to examine the safety, tolerability, dose, and PK of VRC01.23LS alone and in combination with PGT121.414.LS, and PGDM1400LS. The hypothesis is that these regimens will be safe for administration to adults in overall good health and will have a favorable PK profile by intravenous (IV) route.

Adults who are 18-50 years of age and in overall good health will be enrolled. In Part A of the study, VRC01.23LS will be administered alone as a single IV infusion at 5, 20, or 40 mg/kg (Groups 1, 2, and 3). In Part B of the study,

participants will receive 2 doses 6 months apart of VRC01.23LS + PGT121.414.LS + PGDM1400LS administered in combination with weight-based dosing as follows: 5 + 5 + 5 mg/kg IV, 20 + 5 + 5 mg/kg IV, 20 + 20 + 20 mg/kg IV, 40 + 5 + 5 mg/kg IV, and 40 + 40 + 40 mg/kg IV (Groups 4-8). Participants will be followed for 6 months in Part A and 12 months in Part B.

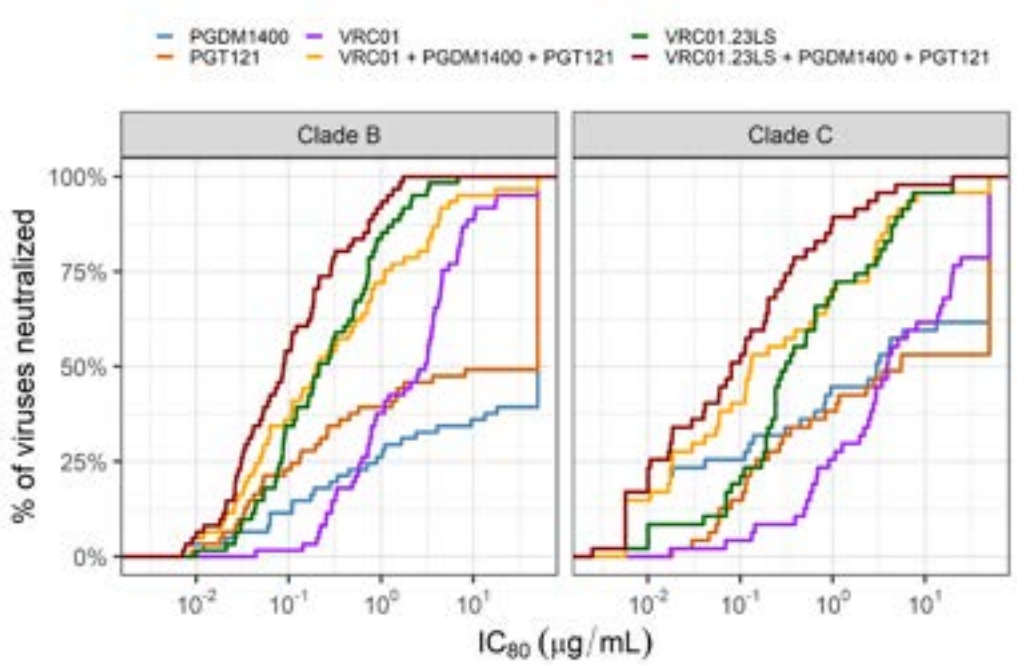

Figure 4-2 Breadth and potency curves for PGT121, PGDM1400, VRC01, VRC01.23LS, and 2 triple combinations (PGT121 + PGDM1400 + VRC01 and PGT121 + PGDM1400 + VRC01.23LS) to a panel of 108 viruses (61 from Clade B and 47 from Clade C) from the placebo arm in the AMP trials.

4.1.2 VRC01.23LS

- The VRC developed VRC01.23LS, a highly potent and broadly neutralizing HIV-1 human bnAb targeted against the HIV-1 CD4bs. Numerous HIV-1 neutralizing bnAbs from the VRC01 family, including VRC01 and VRC07, have now been isolated from the same individual (donor 45) who lived with HIV-1 for more than 15 years and whose immune system controlled the virus without ART (38, 39). Through advances in B-cell immunology and structure-guided optimization techniques, VRC01.23LS was developed with potency and breadth greater than the original VRC01 Ab. VRC01.23LS varies from parent VRC01LS by 3 sets of mutations that were designed to increase neutralization potency and breadth while not contributing to autoreactivity. These mutations include:

- Heavy chain (HC) G54W (glycine to tryptophan at HC residue 54), filling a hydrophobic pocket at the interface between VRC01LS and HIV-1 Env gp120,

- Extended HC Framework 3 (FR3) loop, adopted from VRC01 mAb class member VRC03, that increases contact surface area between the FR3 loop and a neighboring HIV-1 env gp120 protomer. This insertion enhanced neutralizing potency of VRC01-class Abs and reduced autoreactivity (40) and,

- Deletion of the light chain N-terminal-most 3 amino acids to reduce potential steric clashes with the variable V5 region of HIV-1 env gp120.

On a 208 HIV-pseudovirus cross-clade panel, in comparison to VRC01LS, VRC01.23LS exhibits overall ~8-fold greater neutralization potency with a geometric mean IC50 of 0.042 mcg/mL, and 94% breadth at IC50 of < 1 mcg/mL (41). Serum concentrations of VRC01.23LS and VRC01LS in human neonatal Fc-receptor (FcRn) knock-in (KI) mice were comparable (41). Data from a study in cynomolgus macaques support the comparability of VRC01LS and VRC01.23LS PK. VRC01LS has a half-life (t1/2) of 71 ± 18 days in humans, and a comparable human t1/2 is expected for VRC01.23LS. Based on substantial PK data acquired from evaluating the LS mutation incorporated in multiple VRC mAbs, the LS modification has been retained in VRC01.23LS to increase pH-dependent FcRn binding, and hence, to increase Ab half-life in vivo (15, 18, 42)

On a cross-clade panel of 208 viruses, the median IC80 (IC50) of VRC01.23 was 0.107 (0.041) across all samples with IC80 (or IC50) < 50 mcg/mL; 96% of viruses in the panel were neutralized at an IC80 of < 10 mcg/mL and 90% of viruses were neutralized at an IC80 of < 1.0 mcg/mL (Figure 4-3).

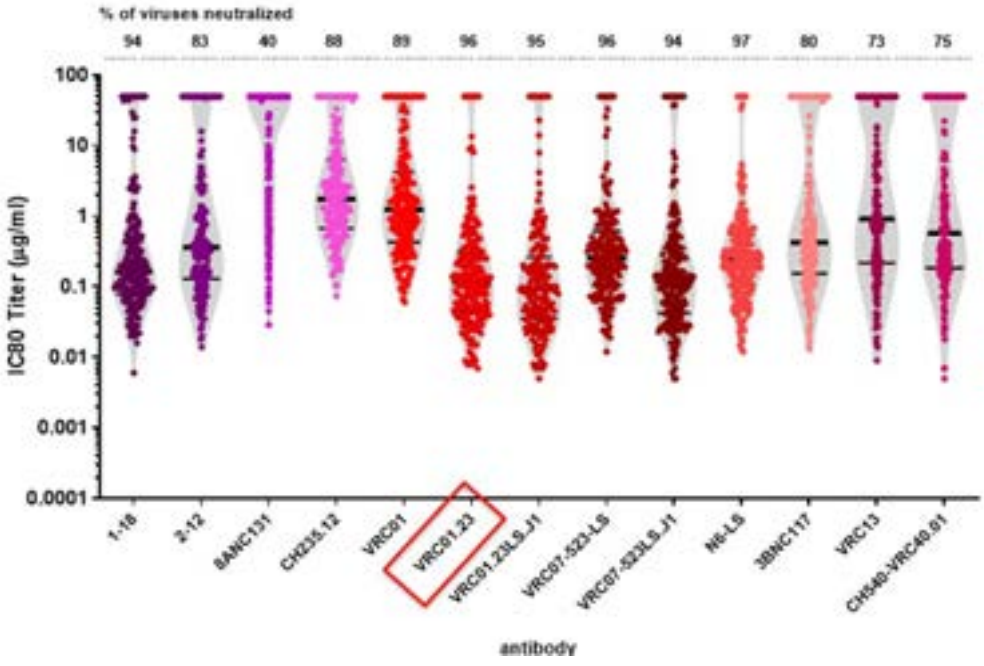

Figure 4-3 Increased potency of chimeric Abs against global HIV-1 isolates. Neutralization titers (IC80, mcg/mL) for CD4bs mAbs against a large global panel of 208 HIV-1 strains of different clades and circulating recombinant forms. The median IC80 value against Ab-sensitive strains is indicated by the thick horizontal line. The thin lines above and below show

quartiles. All neutralization assays were performed in duplicate wells. The percentage of sensitive strains at doses up to 50 mcg/mL is indicated on the top for each Ab.

The LS mutation was introduced by site-directed mutagenesis to increase the binding affinity for the FcRn, resulting in increased recirculation of functional immunoglobin G (IgG) and thereby increasing plasma half-life (41). VRC01.23LS has prolonged half-life that looks similar to VRC01LS in human FcRn transgenic mice and cynomolgus macaques (Figure 4-4). VRC01.23LS also shows superior IC80 compared to VRC07.523.LS and an extended half-life of 70 days compared to a half-life of 42 days in the case of VRC07.523.LS. Accordingly, VRC01.23LS aims to be a next-generation CD4bs Ab with increased potency and breadth relative to the parental VRC01LS, while maintaining an extended half-life and safety and PK profile comparable to VRC01LS, which is why it was selected to replace VRC07-523LS for this study.

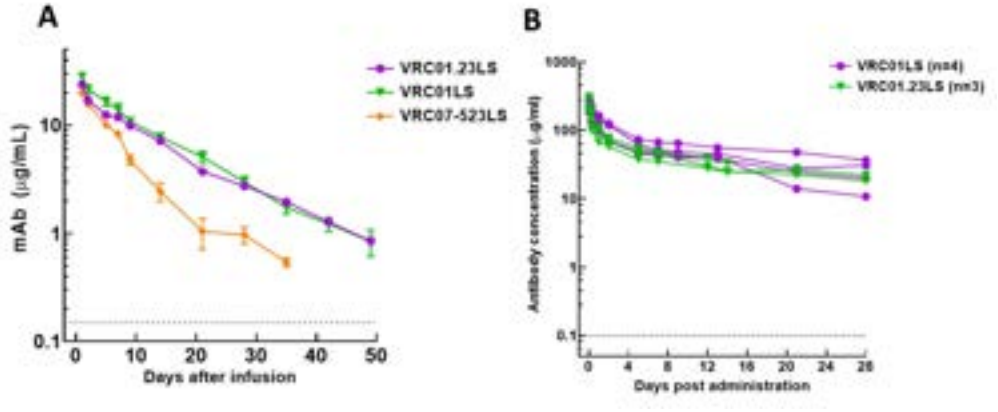

Figure 4-4 VRC01LS and VRC01.23LS Ab PK in (A) human FcRn transgenic mice at a dose of 5mg/kg, IV administration and (B) cynomolgus macaques at a dose 10mg/kg, IV administration

This study will evaluate safety, tolerability, and PK of VRC01.23LS alone and in combination with PGT121.414.LS and PGDM1400LS when given IV. The study also aims to discern whether sera from infused participants retain the same neutralizing breadth with VRC01.23LS alone and in combination with PGT121.414.LS and PGDM1400LS.

4.1.3 PGT121.414.LS

PGT121.414.LS was produced by Just-Evotec Biologics in collaboration with Dan Barouch (Beth Israel Deaconess Medical Center [BIDMC]), and collaborative engagement of CAVD investigators. The drug substance was manufactured under cGMP standards at Just-Evotec Biologics under contract to DAIDS's VTRB. The drug product was filled and released at the VRC Pilot Plant, operated under contract by VCMP, Leidos Biomedical Research, Inc., Frederick, MD. The PGT121.414.LS mAb is an engineered variant of PGT121. It contains a total of 8 residue modifications to improve various aspects of manufacturing, stability and in vivo elimination half-life. Six of the modifications are in the Fragment crystallizable (Fc) region, providing increased conformational stability leading to improved manufacturing characteristics including low pH stability and an improved storage stability profile. The 2 modifications in the Fc region of each

HC are the Xencor Xtend LS modifications, helping provide a significantly reduced elimination half-life in vivo (42, 43). The magnitude and breadth of neutralizing activity of PGT121.414.LS and its parent PGT121 in vitro were shown to be nearly equivalent against a multiclade panel of Env-pseudotyped viruses (Figure 4-5).

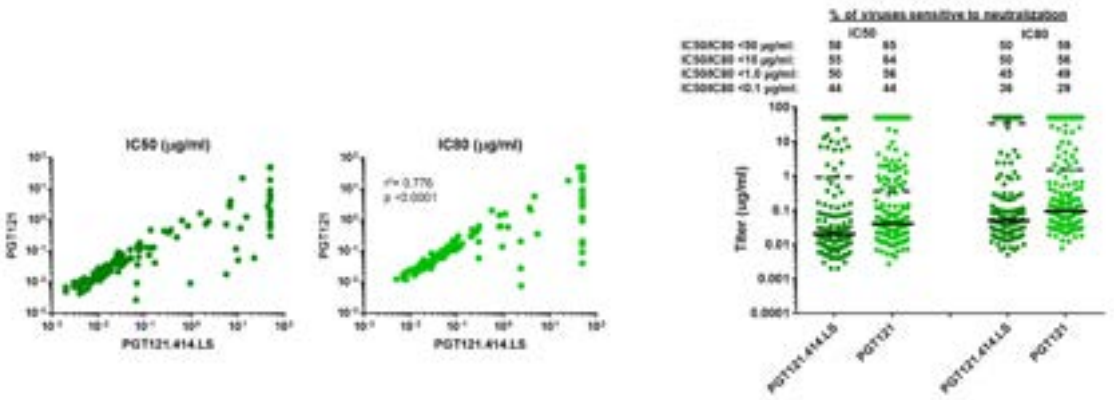

Figure 4-5 Comparison of in vitro neutralizing activity of PGT121 and PGT121.414.LS against a multiclade pseudovirus panel (n = 208). 50 mcg/mL was the highest concentration tested and is used as the cut-off for negative neutralization. Dotted line shows median IC50 and IC80 of all viruses (including those not neutralized). Solid line shows median IC50 and IC80 of viruses sensitive to neutralization (excluding those not neutralized). Data courtesy of the VRC, NIH.

PGT121 was identified from African donor 17 of the International AIDS Vaccine Initiative (IAVI) Protocol G cohort. It targets the V3 glycan-dependent epitope region of the HIV-1 virus. This epitope on the gp120 outer domain includes both protein and glycans and is centered on the conserved residue N332 (44-46). Using a 162-pseudovirus panel, representative of all major HIV-1 circulating clades, the PGT121 had a 10-fold higher median neutralizing potency than mAbs PG9, VRC01, or PGV04 and a 100-fold higher potency than 2G12, b12, or 4E10 (27). While PGT121 neutralized a smaller percentage of the panel of pseudoviruses than VRC01 at an IC50 < 50 mcg/mL (63% for PGT121 vs. 93% for VRC01), it exhibited high potency against the sensitive strains, with neutralization of 44% of the 162-virus panel at an IC50 < 0.1 mcg/mL. This percentage is almost twice the neutralization under the same conditions as PG9, VRC01, PGV04 and 20–40 times more neutralizing than 2G12, b12, and 4E10- all of which have been investigated previously in passive protection studies (27, 45, 47).

4.1.4 PGDM1400LS

PGDM1400 is a broadly neutralizing mAb identified from African donor 84 of the IAVI Protocol G cohort that targets a V2 apex epitope region of HIV-1 Env. PGDM1400LS is an engineered variant of PGDM1400 designed to increase its binding affinity for the FcRn. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the HC constant region far outside of the antigen-combining site (42). As a result of enhanced FcRn function, PGDM1400LS is anticipated to have an extended half-life in both serum and mucosal tissue compared to PGDM1400. Other than the 2 amino acid difference, PGDM1400LS

is identical to PGDM1400. PGDM1400LS drug substance was manufactured under cGMP standards for NIAID by Just–Evotec Biologics, under contract to DAIDS's VTRB. The drug product was filled and released at the VRC Pilot Plant, operated under contract by VCMP.

4.1.5 Cross-network implementation

DAIDS has requested that its 2 major prevention trial Networks—the HVTN and the HPTN—work together in the rapid development of HIV-directed bnAbs for both the advancement of vaccine research and HIV prevention purposes. This priority program leverages the historical partnership between the HVTN and the VRC (a major developer of anti-HIV bnAbs) and other commercial developers, the strong portfolio of biomedical-based HIV prevention trials that the HVTN and HPTN have developed over the past 2 decades, the multidisciplinary expertise of investigators in each Network, and the Networks' complementary laboratory and statistical expertise. In addition, the 2 Networks have complementary CRSs that allow for rapid enrollment of participants, worldwide. The engagement of CRSs from both Networks, particularly in early phase trials, accelerates recruitment, diversifies the trial cohort, and builds capacity for the conduct of future bnAb efficacy trials.

4.2 Trial design rationale

This study aims to evaluate the safety, tolerability, dose, and PK of VRC01.23LS administered IV and in combination with PGDM1400LS, a V2-apex-targeting mAb, and PGT121.414.LS, a V3-glycan-targeting mAb. VRC01.23LS was selected for this study over VRC07-523LS given the improved potency and longer half-life will allow this combination of bnAbs to achieve the neutralization goal associated with 90% efficacy when administered every 24 weeks. The hypothesis is that VRC01.23LS alone and coadministered with PGDM1400LS and PGT121.414.LS will be safe when administered via the IV route to adults in overall good health.

In Part A of the study, VRC01.23LS will be administered via IV infusion at 5, 20, or 40 mg/kg (Groups 1-3). Each group in Part A will have 5 participants. At each of 2 visits in Part B of the study, participants will receive consecutive administration of VRC01.23LS followed by PGDM1400LS and PGT121.414.LS via IV infusions. Five dose combinations are considered in this study: 5 mg/kg each per dose (Group 4); 20 mg/kg of VRC01.23LS paired with 5 mg/kg of PGDM1400LS and 5 mg/kg of PGT121.414.LS per dose (Group 5); 20 mg/kg each per dose (Group 6); 40 mg/kg of VRC01.23LS paired with 5 mg/kg of PGDM1400LS and 5 mg/kg of PGT121.414.LS per dose (Group 7); and 40 mg/kg each per dose (Group 8).

Ideally, the study will demonstrate that (1) VRC01.23LS alone and in combination with PGDM1400LS and PGT121.414.LS is safe and well-tolerated when given via the IV route, (2) the half-life of VRC01.23LS is comparable to

that of VRC01LS and is significantly longer than that of VRC01, (3) the half-life of PGDM1400LS is significantly longer than that of PGDM1400, (4) the half-life of PGT121.414.LS is significantly longer than that of PGT121, (5) the half-life of each mAb is unchanged by coadministration with the other 2 mAbs, and (6) to discern whether sera from participants who received infusions retain the same neutralizing breadth in vitro as VRC01.23LS alone and in combination with PGT121.414LS and PDGM1400LS.

Study safety data reviews and planned holds are detailed in Section 11.3.1 and Table 11-2.

4.2.1 Dose (amount and number)

The dose combinations chosen for the study were based on a meta-analysis of NHP studies (48) and observations of the neutralization potency required to achieve protective efficacy in the AMP trials (37), modeled or projected pharmokakinetics of VRC01.23LS, PGDM1400LS, and PGT121.414.LS, and in vitro neutralization potency of each mAb. Figure 4-6 summarizes how the estimated prevention efficacy varied as the predicted ID80, also referred to as PT80, based on the AMP trials data. AMP studies suggested that achieving an over 80% prevention efficacy would likely require an ID80 of above 200.

Figure 4-7 summarizes the percentage of virus strains for which PT80 > 200 for at least 1 mAb, PT80 > 200 for at least 2 mAbs, and PT80 > 200 for all 3 mAbs in a triple combination at the end of Week 12 and the end of Week 24 under each of the 5 regimens.

Figure 4-8 to Figure 4-12 display the boxplots of mAb-specific (orange, purple and green) predicted serum titer (PT80) for a panel of viruses in the AMP control arm (65 from clade B and 47 from clade C) during the study period (24 weeks) under each of the 5 dose combinations. The blue boxplot in each figure further plots the distribution of triple-bnAb-combined PT80 obtained under the Bliss-Hill model. For instance, under a dose combination of 5 mg/kg VRC01.23LS + 5 mg/kg PGDM1400LS + 5 mg/kg PGT121.414.LS, modeling suggested that by the end of Week 12, triple-mAb-combined PT80 will remain higher than 200 for 70% of clade C viruses and 75% of clade B viruses isolated from the AMP control arm. Under a dose combination of 40 mg/kg VRC01.23LS + 40 mg/kg PGDM1400LS + 40 mg/kg PGT121.414.LS, triple-mAb-combined PT80 will remain higher than 200 for 100% of clade C viruses and 96% clade B viruses by the end of Week 12. Moreover, mAb-specific PT80 will remain larger than 200 for at least 2 mAbs for 55% of clade B virus strains and 49% of clade C virus strains by the end of Week 12.

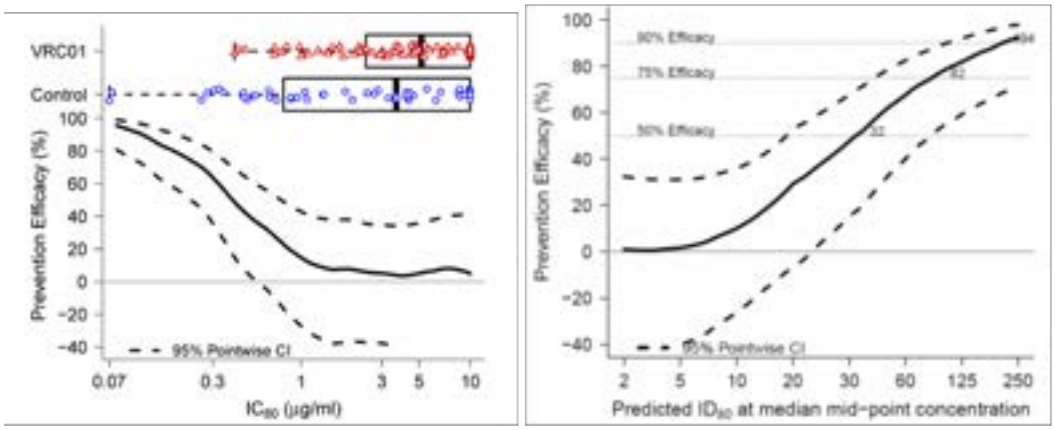

Figure 4-6 Relationship between neutralization titers and level of prevention efficacy. (A) Estimated prevention efficacy (pooled VRC01 groups vs. placebo) at the week 80 visit plotted against the quantitative IC80 of the acquired virus. A red triangle indicates an acquired virus in the designated VRC01 group, and a blue circle an acquired virus in the placebo group. (B) Estimated prevention efficacy by PT80 (predicted ID80 serum neutralization titer). This plot repeats the panel (A) result except that it scales the x-axis by the median mid-infusion visit concentration of VRC01. The median concentration was calculated based on the n = 82 noncases sampled for PK modeling.

	BH-Combined		At Least One		VRC01.23LS		PGDM1400LS		PGT121.414.LS		At Least Two		All Three	
	$PT_{80} > 200$		$PT_{80} > 200$		$PT_{80} > 200$		$PT_{80} > 200$		$PT_{80} > 200$		$PT_{80} > 200$		$PT_{80} > 200$	
Clade	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24
5 mg/kg + 5 mg/kg + 5 mg/kg														
Clade B	75%	59%	66%	42%	48%	23%	15%	12%	25%	15%	20%	9%	2%	0%
Clade C	70%	47%	60%	43%	32%	17%	32%	26%	15%	4%	17%	4%	2%	0%
20 mg/kg + 5 mg/kg + 5 mg/kg														
Clade B	89%	78%	86%	69%	80%	57%	15%	12%	25%	15%	32%	15%	2%	0%
Clade C	81%	66%	77%	60%	66%	49%	32%	26%	15%	4%	32%	19%	4%	0%
20 mg/kg + 20 mg/kg + 20 mg/kg														
Clade B	92%	82%	89%	79%	80%	57%	23%	19%	37%	31%	46%	25%	5%	3%
Clade C	85%	79%	83%	70%	66%	49%	36%	32%	34%	26%	40%	32%	13%	4%
40 mg/kg + 5 mg/kg + 5 mg/kg														
Clade B	97%	83%	94%	77%	89%	69%	15%	12%	25%	15%	34%	20%	2%	0%
Clade C	87%	72%	79%	68%	72%	60%	32%	26%	15%	4%	36%	21%	4%	0%
40 mg/kg + 40 mg/kg + 40 mg/kg														
Clade B	100%	88%	97%	85%	89%	69%	29%	23%	42%	37%	55%	42%	8%	3%
Clade C	96%	85%	87%	81%	72%	60%	45%	36%	36%	32%	49%	34%	17%	13%

Figure 4-7 Percentage of virus strains for which the Bliss-Hill-combined PT80 > 200, VRC01.23LS-specific PT80 > 200, PGDM1400LS-specific PT80 > 200, and PGT121.414.LS-

specific PT80 > 200, PT80 > 200 for at least 1 mAb, PT80 > 200 for at least 2 mAbs, and PT80 > 200 for all 3 mAbs.

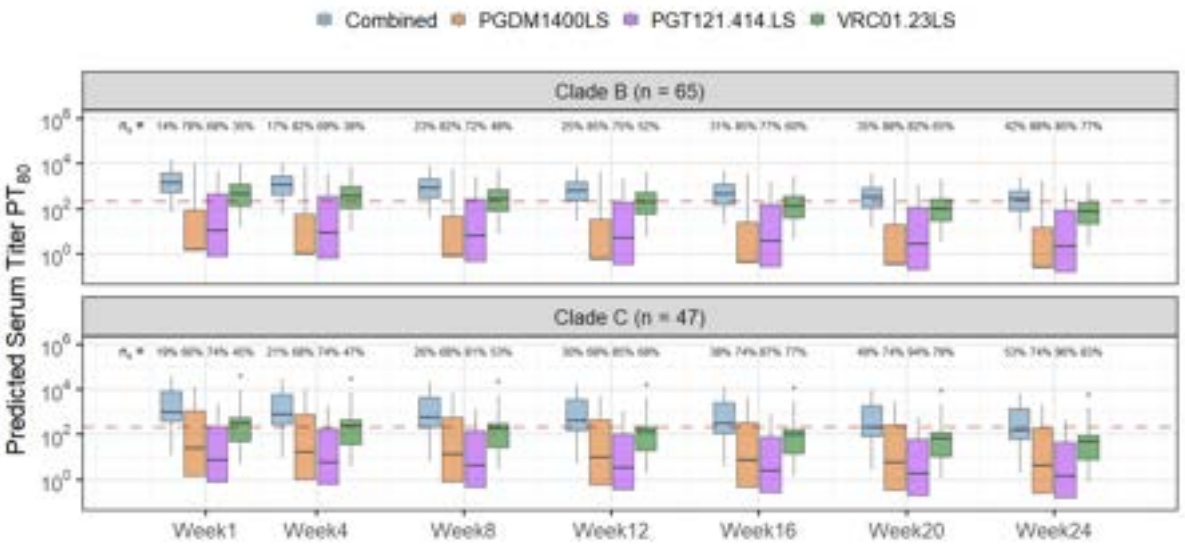

Figure 4-8 Boxplots of mAb-specific (orange, purple and green) and triple-mAb-combined (blue) predicted serum titer (PT80) for a panel of viruses in the AMP control arm (65 from clade B and 47 from clade C) during the study period (24 weeks) under the dose combination of **5 mg/kg VRC01.23LS + 5 mg/kg PGDM1400LS + 5 mg/kg PGT121.414.LS**. The combination PT80 was obtained under the Bliss-Hill model. n_s = Number of viral strains below whose mAb-specific (or combo-mAb-specific) PT200 is below 200.

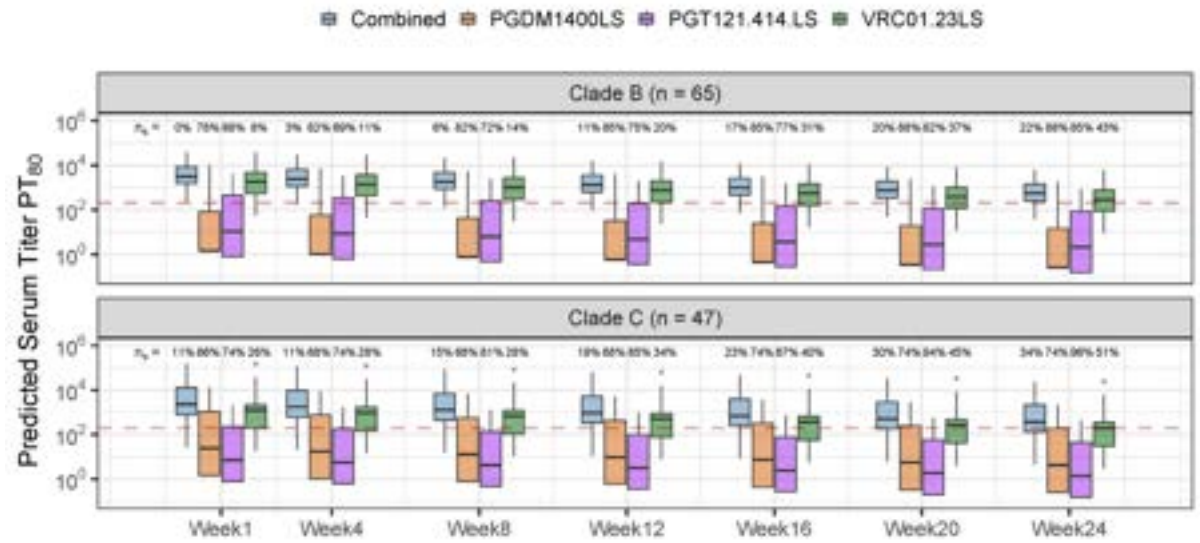

Figure 4-9 Boxplots of mAb-specific (orange, purple and green) and triple-mAb-combined (blue) predicted serum titer (PT80) for a panel of viruses in the AMP control arm (65 from clade B and 47 from clade C) during the study period (24 weeks) under the dose combination of **20 mg/kg VRC01.23LS + 5**

mg/kg PGDM1400LS + 5 mg/kg PGT121.414.LS. The combination PT80 was obtained under the Bliss-Hill model. n_s = Number of viral strains below whose mAb-specific (or combo-mAb-specific) PT200 is below 200.

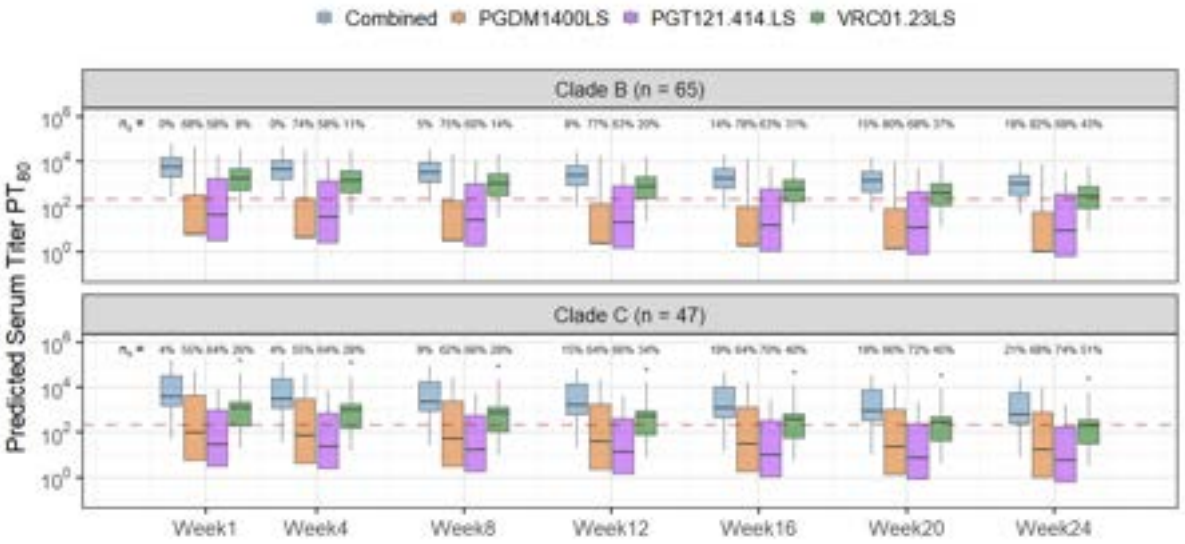

Figure 4-10 Boxplots of mAb-specific (orange, purple and green) and triple-mAb-combined (blue) predicted serum titer (PT80) for a panel of viruses in the AMP control arm (65 from clade B and 47 from clade C) during the study period (24 weeks) under the dose combination of **20 mg/kg VRC01.23LS + 20 mg/kg PGDM1400LS + 20 mg/kg PGT121.414.LS**. The combination PT80 was obtained under the Bliss-Hill model. n_s = Number of viral strains below whose mAb-specific (or combo-mAb-specific) PT200 is below 200.

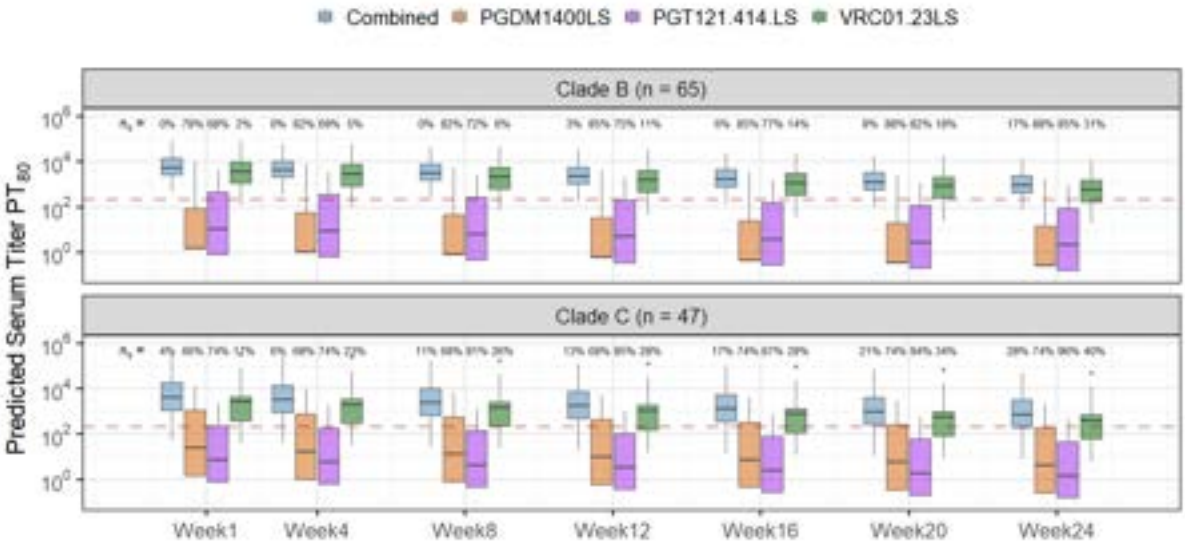

Figure 4-11 Boxplots of mAb-specific (orange, purple and green) and triple-mAb-combined (blue) predicted serum titer (PT80) for a panel of viruses in the AMP control arm (65 from clade B and 47 from clade C) during the study period (24 weeks) under the dose combination of **40 mg/kg VRC01.23LS + 5 mg/kg**

PGDM1400LS + 5 mg/kg PGT121.414.LS. The combination PT80 was obtained under the Bliss-Hill model. n_s = Number of viral strains below whose mAb-specific (or combo-mAb-specific) PT200 is below 200.

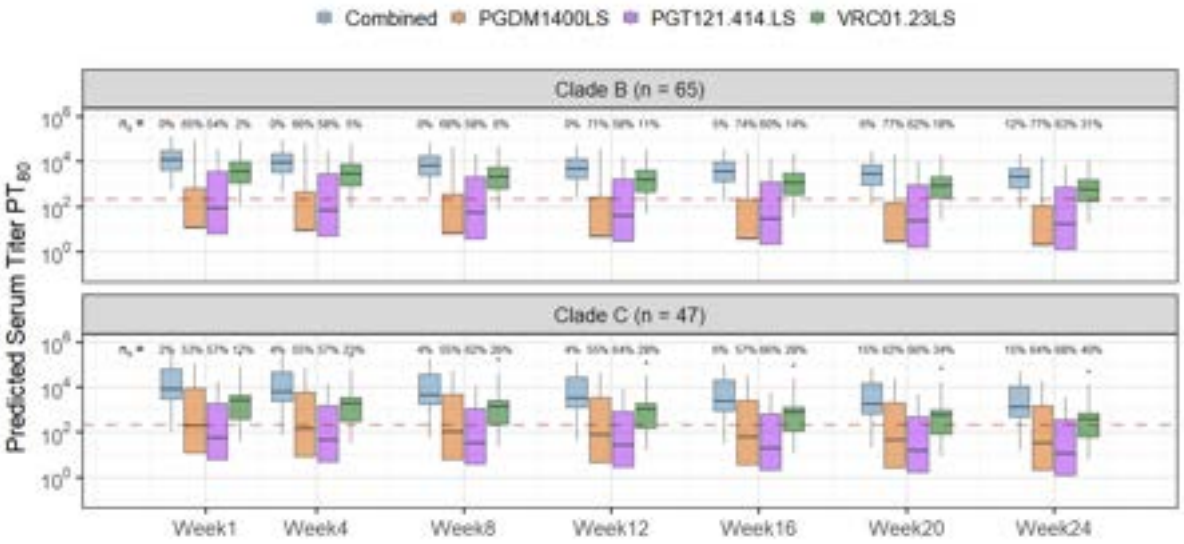

Figure 4-12 Boxplots of mAb-specific (orange, purple and green) and triple-mAb-combined (blue) predicted serum titer (PT80) for a panel of viruses in the AMP control arm (65 from clade B and 47 from clade C) during the study period (24 weeks) under the dose combination of **40 mg/kg VRC01.23LS + 40 mg/kg PGDM1400LS + 40 mg/kg PGT121.414.LS**. The combination PT80 was obtained under the Bliss-Hill model. n_s = Number of viral strains below whose mAb-specific (or combo-mAb-specific) PT200 is below 200.

4.2.2 Schedule

There is currently no human PK data on VRC01.23LS, PGDM1400LS or PGT121.414.LS given in combination. The PK modeling was based on that of PGDM1400, PGT121, and VRC01LS in combination, assuming no drug-drug PK interactions. Specifically, the PK modeling of PGDM1400LS and PGT121.414.LS was based on the PK dynamics of PGDM1400 (estimated from n = 18 participants without HIV for PGDM1400 in Barouch 693 [T002]) and PGT121 (estimated from n = 16 participants without HIV for PGT121 in Barouch 628 [T001]) except that we assumed an extended half-life of 70 days. A 70-day half-life of PGDM1400LS and PGT121.414.LS was informed by the PGDM1400LS preclinical PK data, including in FcRn mouse and NHP models, PGT121.414.LS PK data from Part A of the ongoing HVTN 136/HPTN 092 clinical trial, and PGDM1400LS and PGT121.414.LS PK data from the ongoing trial HVTN 140/HPTN 101 clinical trial. The half-lives of the LS variants of PGDM1400 and PGT121 are predicted to be two- to three-fold longer compared to their parental forms. The PK modeling of VRC01.23LS was based on the PK data of VRC01LS, which was estimated to have a half-life of 71 ± 18 days in humans. In addition, linear PK was assumed for the mAbs so that PK parameters estimated based on single-dose settings carried forward to multiple-dose settings. Figure 4-13 plots the mean drug concentration of each mAb following an IV infusion at 5 mg/kg or 40 mg/kg each during the first 24 weeks. In these simulations, we have assumed an average weight of 70 kg.

According to the PK modeling, at 24 weeks following the IV infusion at a dose level of 5 mg/kg each, the serum concentration of each mAb was predicted to be approximately 10 mcg/mL for each mAb (top panel of Figure 4-13). At 24 weeks following the IV infusion at a dose level of 40 mg/kg each, the serum concentration of each mAb was predicted to be above 100 mcg/mL for each mAb (bottom panel of Figure 4-13). Given the IC50 and IC80 data of the mAbs, these PK simulation results suggest that the proposed study design would attain desirable serum concentration levels over time that confer sufficient neutralization against diverse panels of viruses (see Section 4.2.1). The limit of detection of the currently used anti-idiotypic enzyme-linked immunosorbent assay (ELISA) for mAb serum concentrations is 1 mcg/mL. Based on currently available data and knowledge, a dosing interval of every 6 months could attain a serum concentration that is above the limit of detection for all 3 mAbs in the study.

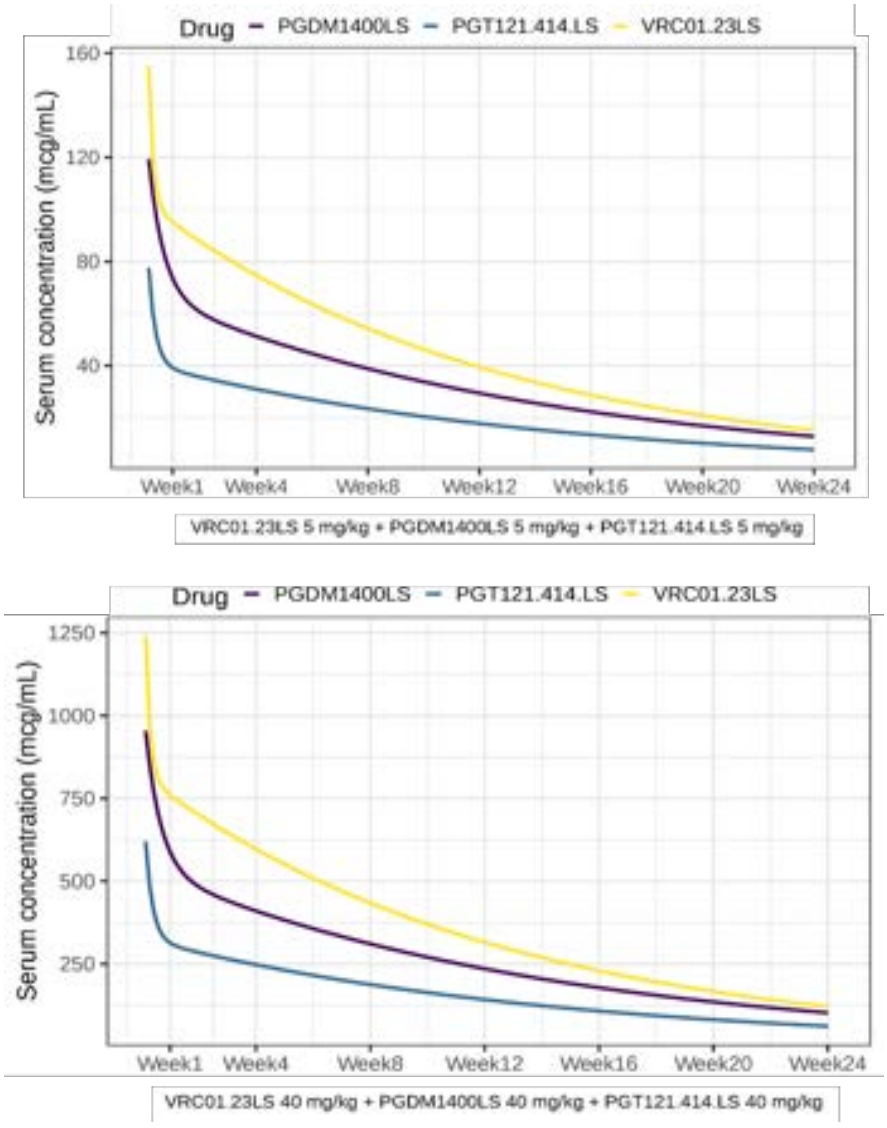

Figure 4-13 Predicted PGDM1400LS, PGT121.414.LS and VRC01.23LS concentration during the first 24 weeks after an IV infusion at 5 mg/kg each (top panel) and at 40 mg/kg each (bottom panel) for a 70-kg person

4.3 Preclinical studies

4.3.1 Preclinical studies of VRC01.23LS

A summary of nonclinical studies conducted with VRC01.23LS is presented in the table below.

Table 4-1 Nonclinical studies conducted with VRC01.23LS

Study purpose	Study Outcome
In vitro neutralization activity (Section 4.3.1.1)	On a 208 HIV-pseudovirus cross-clade panel, in comparison to VRC01, VRC01.23LS exhibits an overall ~8-fold greater neutralization potency with a geometric mean IC50 of 0.042 mcg/mL, and 94% breadth at IC50 of < 1 mcg/mL.
VRC01.23LS serum levels in Mice (Section 4.3.1.2)	In human FcRn transgenic mice, VRC01.23LS exhibited a serum t1/2 comparable to that of parental VRC01LS.
NHP PK (Section 4.3.1.3)	Three cynomolgus monkeys received a single IV dose of 10 mg/kg VRC01.23LS. Two of the monkeys exhibited PK comparable to that of parental VRC01LS. One monkey exhibited depletion beginning on day 20, suggesting induction of an antidrug antibody (ADA) response. No signs of toxicity were observed.
Tissue cross-reactivity (TCR) study (Section 4.3.1.4)	In a Good Laboratory Practice (GLP) TCR study evaluating a panel of 38 normal human tissues obtained from at least 3 adult donors per tissue, VRC01.23LS did not exhibit specific cell membrane binding in any human tissue, which was expected and was consistent with similar lack of binding observed for VRC01 and VRC01LS.
Autoreactivity by assessment of binding to a human epithelial cell line (HEp-2) by indirect immunohistochemistry (Section 4.3.1.5)	VRC01.23LS demonstrated no evidence of autoreactivity as assessed by HEp-2 cell binding.
Autoreactivity by assessment of anti-phospholipid reactivity (Section 4.3.1.6)	VRC01.23LS was considered not reactive in the cardiolipin binding assay when compared to an anti-HIV neutralizing mAb (4E10), known to react with phospholipids.

4.3.1.1 In Vitro Neutralization Activity.

To fully assess and compare the neutralization profile of VRC01.23LS to VRC01 mAb class members, a neutralization assay was conducted on a cross-clade panel of 208 HIV-1 pseudoviruses (Figure 4-14). VRC01.23LS neutralized 94% of the virus tested with a geometric mean IC50 of < 1 mcg/ml, while VRC01 neutralized 74% of the viruses tested with a geometric mean IC50 of < 1 mcg/ml. Using an IC80 cut-off value of < 1.0 mcg/mL, the panel neutralization percentages were 90 and 46 for VRC01.23LS and VRC01, respectively. Overall, in comparison to VRC01, VRC01.23LS exhibits ~8-fold increased neutralization potency with a geometric mean IC50 of 0.042 mcg/mL, and 94% breadth at IC50 of < 1 mcg/mL.

IC_{50} (µg/mL)		
mAb	VRC01	VRC01.23LS
Total Viruses Neutralized at Specified Cut-off Concentration		
IC_{50} < 50 µg/mL	188	200
IC_{50} < 10 µg/mL	187	200
IC_{50} < 1.0 µg/mL	154	196
IC_{50} < 0.1 µg/mL	42	152
IC_{50} < 0.01 µg/mL	0	21
Percent Viruses Neutralized at Specified Cut-off Concentration		
IC_{50} < 50 µg/mL	90	96
IC_{50} < 10 µg/mL	90	96
IC_{50} < 1.0 µg/mL	74	94
IC_{50} < 0.1 µg/mL	20	73
IC_{50} < 0.01 µg/mL	0	10
Median IC_{50}	0.303	0.041
Geometric Mean IC_{50}	0.315	0.042

IC_{80} (µg/mL)		
mAb	VRC01	VRC01.23LS
Total Viruses Neutralized at Specified Cut-off Concentration		
IC_{80} < 50 µg/mL	185	200
IC_{80} < 10 µg/mL	172	199
IC_{80} < 1.0 µg/mL	95	188
IC_{80} < 0.1 µg/mL	5	94
IC_{80} < 0.01 µg/mL	0	7
Percent Viruses Neutralized at Specified Cut-off Concentration		
IC_{80} < 50 µg/mL	89	96
IC_{80} < 10 µg/mL	83	96
IC_{80} < 1.0 µg/mL	46	90
IC_{80} < 0.1 µg/mL	2	45
IC_{80} < 0.01 µg/mL	0	3
Median IC_{80}	0.959	0.107
Geometric Mean IC_{80}	1.064	0.120

Figure 4-14 VRC01.23LS IC50 and IC80 Neutralization Potency and Breadth on 208 Multi-clade Pseudovirus Panel

4.3.1.2 VRC01.23LS Serum Levels Study in Mice

The VRC01.23LS serum levels profile was compared to that of parental VRC01LS using a human FcRn mouse model (41). Mice received a single 5 mg/kg dose of VRC01LS or VRC01.23LS by IV, and sera mAb titers were assessed over seven weeks. In separate experiments, VRC01.23LS and VRC01LS maintained comparable titers, both of which were higher than those of two other VRC mAbs against the CD4bs, N6LS and VRC07-523LS (Figure 4-15)

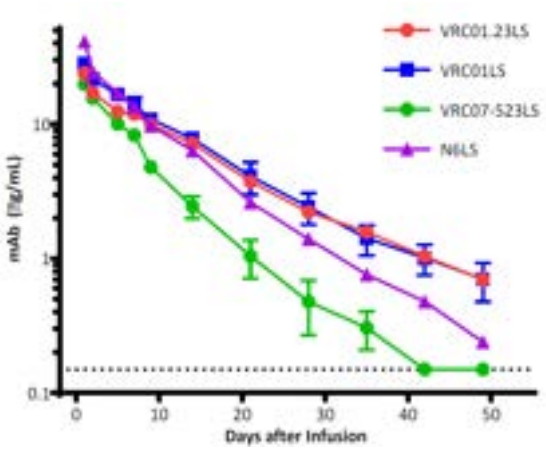

Figure 4-15 VRC01.23LS Serum Levels in human FcRn Mice

4.3.1.3 VRC01.23LS PK Study in Cynomolgus Macaques

The VRC evaluated the in vivo PK profile of development-grade VRC01.23LS made using process-representative of the manufacturing methods used for the GMP drug product, in one female and two male Cynomolgus macaques. The

antibody was given as a single 10 mg/kg IV injection via manual push over 3-4 minutes. Blood was collected for PK evaluation post-dose at 5 and 30 minutes; 6 hours; days 1, 2, 5, 7, 12, and 14; and weekly up to 12 weeks after administration, and titers were quantitated by anti-idiotype based ELISA. Figure 4-16 shows the serum levels of VRC01.23LS in each animal. In two animals, H555 and HALW, levels of VRC01.23LS were maintained above 1 mcg/mL up to day 84 post infusion with a very gradual decline over time. The third animal, H59G (male), exhibited a more rapid decline in antibody levels, reaching undetectable levels by day 28 post infusion, attributed to an antidrug antibody (ADA) response. As shown in Table 4-2, the average t1/2 was calculated to be 20.9 days with a range of 10.2 to 31.4 days. The average area under the curve (AUC) was 1249 Day*mcg/mL with a range of 667 to 1922 Day*mcg/mL. The average clearance was 9.6 mL/Day/kg with a range of 5.2 to 15.0 mL/Day/kg.

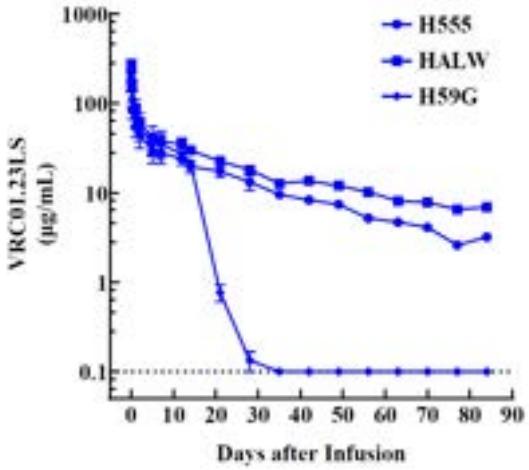

Figure 4-16 Serum levels of VRC01.23LS antibody in three Cynomolgus macaques administered a single dose of 10 mg/kg via the IV route

Clinical signs were evaluated daily; no abnormal clinical signs were noted. Pre-dose and at each post-dose PK time point: animals were weighed, body temperature was measured, blood was collected for hematology and clinical chemistry, and urine was collected for urinalysis. Compared to pre-dose baseline, no differences were detected post-dose.

Table 4-2 In vivo PK parameters for VRC01.23LS in three Cynomolgus macaques administered a single dose of 10 mg/kg via the IV route

Antibody	Animal ID	Half-life	AUC	Clearance	C_{max}	Serum Ab conc at day 14
		Day	Day*µg/mL	mL/Day/kg	(µg/mL)	(µg/mL)
VRC01.23LS	H555	21.1	1159	8.6	167.1	19.6
	HALW	31.4	1922	5.2	266.1	29.8
	H59G	10.2	667	15.0	203.9	21.8
Average		*20.9*	*1249*	*9.6*	*212.3*	*23.7*
Standard error		*6.1*	*365*	*2.9*	*28.9*	*3.1*

4.3.1.4 Toxicology

No Good Laboratory Practice (GLP) toxicology study has been conducted with VRC01.23LS. In the tissue cross-reactivity (TCR) study with adult human tissues (se Investigator's Brochure [IB] for details), no membrane binding was detected. In the absence of an endogenous target, VRC01.23LS is expected to have a safety profile consistent with VRC01.LS and the VRC01 mAb class. See Investigator's Brochure [IB] for details).

4.3.1.5 VRC01.23LS Assessment of Binding to a Human Epithelial Cell Line (HEp-2) by Immunochemistry

VRC01.23LS was evaluated for autoreactivity by human epithelial type 2 (HEp-2) cell staining. Control and test mAbs were analyzed at 25 mcg/mL. Compared to anti-HIV-1 Env mAb controls, parental VRC01LS and 4E10 (Figure 4, Panel 2 and Panel 3, respectively), VRC01.23LS, at 25 mcg/mL (Figure 4-17), scored as zero for fluorescent staining by this assay, suggesting low potential for autoreactivity (from IB, 1). VRC01.23LS demonstrated no evidence of autoreactivity as assessed by HEp-2 cell binding.

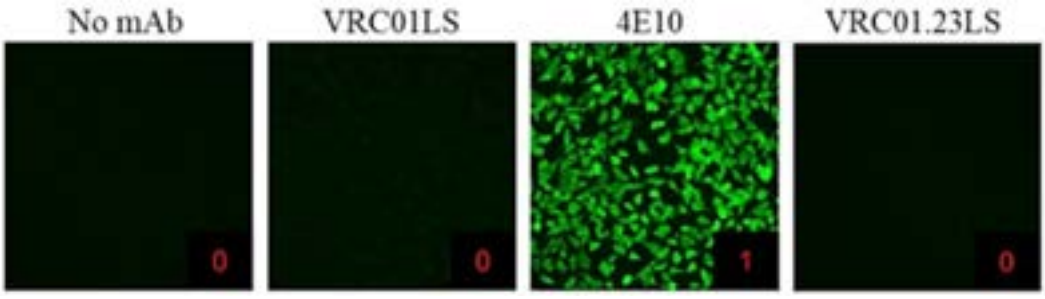

Figure 4-17 VRC01.23LS HEp-2 Cell Staining by Indirect Immuno Fluorescence

4.3.1.6 VRC01.23LS Autoreactivity by Semi-Quantitative Anti-cardiolipin ELISA

VRC01.23LS autoreactivity was assessed orthogonally by a semi-quantitative anti-cardiolipin ELISA assay (41). In this assay, cardiolipin is coated in plate wells, and mAbs are tested in serial three-fold dilutions for binding to cardiolipin.

4E10, an anti-HIV neutralizing antibody (nAb) known to react with phospholipids, was used as a positive control. IgG phospholipid (GPL) units were calculated from optical density (OD) measurements using a standard curve. GPL score < 20 was considered as not reactive, 20-80 as low positive, and > 80 as high positive. VRC01.23LS's score was negative. 4E10 scored high positive (Table 4-3). VRC01.23LS was considered not reactive in the cardiolipin binding assay.

Table 4-3 VRC01.23LS Binding to Cardiolipin by ELISA

mAb / mAb conc.	GPL units			
	100 µg/ml	33.3 µg/ml	11.1 µg/ml	3.7 µg/ml
VRC01LS	-4.83	-4.74	-4.30	-4.88
4E10	225.70	240.31	239.16	227.82
VRC01.23LS	15.62	2.47	-2.91	-4.31
Blank	0			
Scoring key	White shading: <20: No Reactivity			
	Yellow shading: 20-80: Low Positive			
	Red shading: >80: High Positive			

4.3.2 Preclinical studies of PGT121.414.LS

Preclinical studies of PGT121.414.LS include: humanized FcRn mouse PK, NHP PK, repeat-dose toxicity and TCR, as detailed below.

4.3.2.1 PK study of PGT121.414.LS in human FcRn transgenic mice

The VRC, NIAID, and NIH evaluated the in vivo PK profile of PGT121.414.LS in 3 human FcRn transgenic mice (49). In this study, they tested PGT121.414.LS (lot #S-20190121-1) produced from a stably transfected Chinese hamster ovary (CHO) cell line. The Ab was given at a single bolus dose of 10 mg/kg via the IV route. The levels of Ab in the sera of these animals at various timepoints up to 28 days after administration were then quantitated by an anti-PGT121 idiotype based ELISA method. Figure 4-18 shows the sera levels of PGT121.414.LS in each animal, with levels maintained above 10 mcg/mL up to day 9 postinfusion in all animals. After day 9, the sera levels of PGT121.414.LS steeply dropped to below the detection limit in 2 out of the 3 animals indicative of an ADA response against PGT121.414.LS in those animals. The third animal showed a longer persistence of the Ab in the sera with levels dropping below the detection limit at day 28 postinfusion.

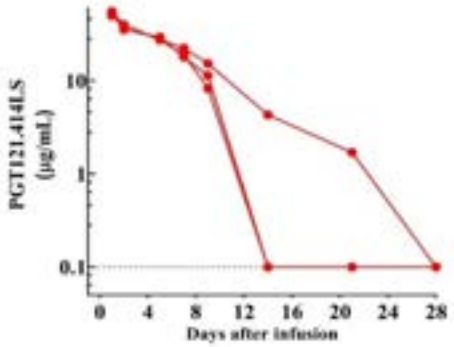

Figure 4-18 Sera levels of PGT121.414.LS Ab in 3 human FcRn transgenic mice administered 10 mg/kg of the Ab via the IV route.

The PK parameters were calculated using a noncompartment model in the WinNonLin software package and are presented in

Table 4-4. The average half-life was calculated to be 3.61 days with a range of 2.53 to 4.59 days. The average AUC was calculated to be 332*day mcg/mL with a range of 312 to 368*day mcg/mL. The average clearance (CL) was calculated to be 15.13 mL/day/kg with a range of 13.58 to 15.99 mL/day/kg.

Table 4-4 In vivo PK parameters for PGT121.414.LS in human FcRn transgenic mice

Ab	Animal ID	Half-life (days)	AUC (day*mcg/mL)	CL mL/day/kg
PGT121.414LS	2283	4.59	368	13.58
	2284	3.70	315	15.82
	2285	2.53	312	15.99
Average		**3.61**	**332**	**15.13**
Standard error		**0.46**	**14**	**0.60**

4.3.2.2 PK study of PGT121.414.LS in rhesus macaques

The VRC evaluated the in vivo PK profile of PGT121.414.LS in 4 male and 2 female rhesus macaques. In this study, we tested PGT121.414.LS (lot #S-20190121-1) produced from a stably transfected CHO cell line. The Ab was given at a single bolus dose of 10 mg/kg via either the subcutaneous (SC) (n = 3) or IV route (n = 3). The levels of Ab in the sera of these animals at various timepoints up to 105 days after administration were then quantitated by an anti-PGT121 idiotype based ELISA method. Figure 4-19 shows the sera levels of PGT121.414.LS in each animal. The initial sera Ab levels were higher when the Ab was given IV compared to SC, but by day 2, the sera Ab levels were similar in all animals irrespective of route and followed similar distribution over time Also, sera Ab levels were maintained above 5 mcg/mL for up to 105 days after dosing in all animals, irrespective of route. In addition, none of the animals developed ADA responses against PGT121.414.LS in this study.

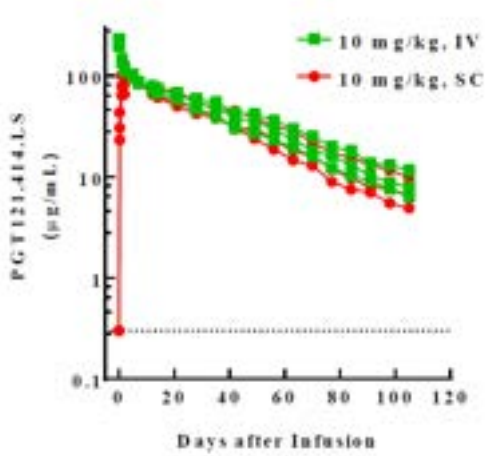

Figure 4-19 Sera levels of PGT121.414.LS Ab in 6 rhesus macaques administered at 10 mg/kg of the Ab via either the SC or IV route.

The PK parameters were calculated using a noncompartment model in the WinNonLin software package and are presented in Table 4-5. The average half-life for PGT121.414.LS was 28.4 days for the IV route and 27.8 days for the SC route, which were very similar to each other, with a range of 26.6 days to 31.9 days. The AUC was slightly higher for the IV route (4710 day*mcg/mL) than for the SC route (3617 day*mcg/mL) due to the higher initial peak observed in the serum levels for the IV route compared to the SC route. The CL was similar between the 2 routes (2.24 mL/day/kg for IV versus 2.61 mL/day/kg for SC).

Table 4-5 In vivo PK parameters for PGT121.414.LS in rhesus macaques

Route	Animal ID	Half-life (days)	AUC (day*mcg/mL)	CL (mL/day/kg)
IV	0DG	26.80	4221	2.22
IV	DGFH	26.65	3702	2.54
IV	DGKX	31.91	4586	1.96
	Average	**28.45**	**4170**	**2.24**
	Standard error	**1.73**	**257**	**0.17**
SC	09Z	30.13	4223	2.15
SC	DGDW	27.73	3353	2.78
SC	DGFK	25.53	3274	2.90
	Average	**27.80**	**3617**	**2.61**
	Standard error	**1.33**	**304**	**0.23**

4.3.2.3 Good Laboratory Practice (GLP) repeat dose IV or SC of PGT121.414.LS in rats

PGT121.414.LS was tested in a GLP-compliant study to determine the potential toxicity and toxicokinetics of the mAb in Sprague Dawley rats after 3 IV or SC dose administrations at 10-day intervals (on Days 1, 11, and 21) followed by a recovery period. No clinically significant findings were noted in the toxicology study. The study details and results are included in the IB.

4.3.2.4 PGT121.414.LS TCR study

PGT121.414.LS was tested in a GLP-compliant study to determine the potential cross reactivity of the mAb in human tissue cryosections. The TCR study was conducted using a panel of normal human tissue cryosections from 3 separate donors, according to recommendations in the Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (CBER 1997) and consistent with ICH guidance S6(R1). No clinically significant findings were noted in the TCR study. The study details and results are included in the IB.

4.3.2.5 PGT121.414.LS preclinical functional studies

PGT121.414.LS was recently assayed against a multiclade panel of 208 Env-pseudoviruses at the VRC (Table 4-6). As expected, it had less breadth than VRC07-523LS and VRC01 but was approximately 4-times more potent than VRC07-523LS and 10-times more potent than VRC01 against the viruses that were neutralized.

Table 4-6 Neutralization data of mAbs assayed against VITL/VRC multiclade panel

VITL/VRC Multiclade Panel

IC50	PGT121.414 LS	PGT121	VRC01	VRC01.23	VRC07-523-LS	N6-LS	10-1074	PGDM1400	10E8v4
# Viruses	208	208	208	208	208	208	208	208	208
% VS Neutralized									
IC50 <50ug/ml	58	65	90	96	96	98	63	80	98
IC50 <10ug/ml	55	64	89	96	96	97	63	79	98
IC50 <1.0ug/ml	50	56	72	94	92	95	60	75	71
IC50 <0.1ug/ml	44	44	17	73	53	63	42	60	15
For Sensitive Viruses Only:									
Median IC50	0.022	0.040	0.328	0.041	0.081	0.069	0.054	0.014	0.463
Geometric Mean	0.044	0.072	0.339	0.042	0.088	0.072	0.060	0.024	0.419
For All Viruses:									
Median IC50	0.904	0.352	0.392	0.042	0.086	0.071	0.204	0.043	0.468
Geometric Mean	0.868	0.691	0.548	0.055	0.116	0.081	0.724	0.107	0.470

IC80	PGT121.414 LS	PGT121	VRC01	VRC01.23	VRC07-523-LS	N6-LS	10-1074	PGDM1400	10E8v4
# Viruses	208	208	208	208	208	208	208	208	208
% VS Neutralized									
IC80 <50ug/ml	50	59	89	96	96	97	60	74	98
IC80 <10ug/ml	50	56	83	96	94	96	59	72	89
IC80 <1.0ug/ml	45	49	46	90	83	88	52	63	26
IC80 <0.1ug/ml	36	29	2	45	23	23	26	44	3
For Sensitive Viruses Only:									
Median IC80	0.051	0.099	0.959	0.107	0.238	0.221	0.126	0.047	2.31
Geometric Mean	0.076	0.154	1.06	0.120	0.257	0.231	0.157	0.069	1.91
For All Viruses:									
Median IC80	33.3	1.50	1.24	0.117	0.257	0.235	0.884	0.201	2.36
Geometric Mean	1.89	1.68	1.63	0.151	0.323	0.270	1.57	0.394	2.06

See IB for further details.

4.3.3 Preclinical studies of PGDM1400LS

4.3.3.1 Preclinical study in rhesus macaques (Sanofi, VRC, BIDMC, Ragon Institute, Scripps, NIAID)

In 2017, L. Xu et al reported in Science (50) on the development of broadly neutralizing trispecific Abs to HIV-1. Trispecific Abs combine the specificities against 3 distinct epitopes on the HIV-1 Env into a single molecule; one of these epitopes is the V2 binding site of PGDM1400. LS mutations were engineered into the trispecific molecules as well as the parental Abs, including PGDM1400. As shown in Figure 4-20, plasma Ab levels in rhesus macaques administered 5 mg/kg IV of PGDM1400LS are comparable to those of VRC01LS, which has a published half-life in humans of 71 ± 18 days (51), and as depicted in Figure 4-20C, 3 Ab specificities were required to prevent viremia in 100% of rhesus macaques challenged with a mixture of SHIV BaLP4 and SHIV 325c.

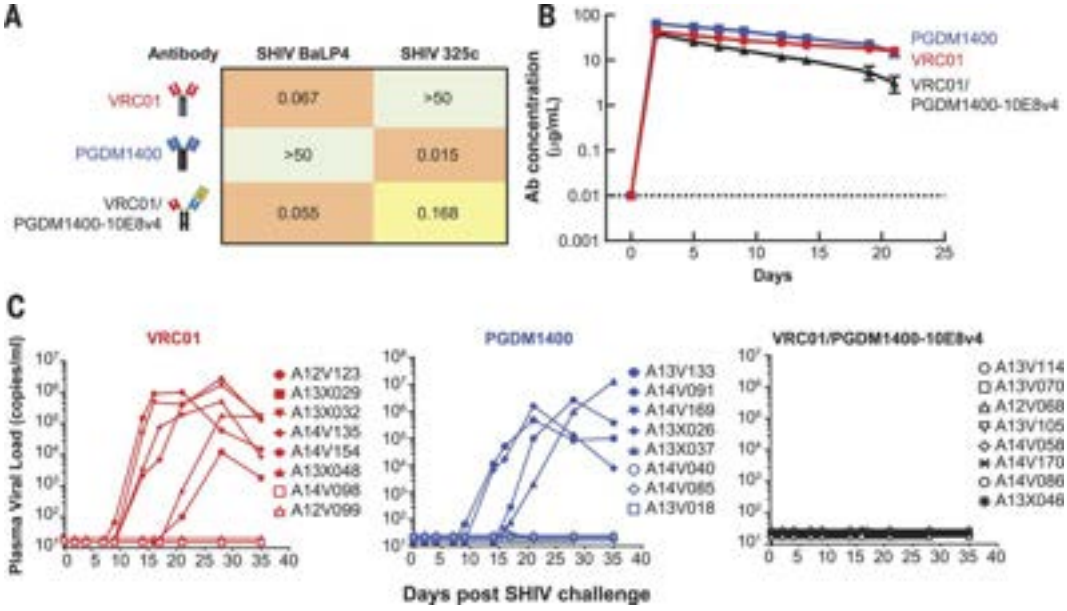

Figure 4-20 Trispecific and bnAb sensitivity of SHIVs, plasma Ab levels, and viremia in rhesus macaques. All Abs in the figure are LS variants. (A) The IC50 neutralizing titers (mcg/ml) of VRC01, PGDM1400, and VRC01/10E8v4-PGDM1400 against replication competent SHIV BaLP4 or SHIV 325c. (B) Plasma levels of VRC01, PGDM1400 and VRC01/PGDM1400-10E8v4 in rhesus macaques (n = 8 on each arm, done in 2 separate experiments with 4 animals each). All animals were administered 5 mg/kg of the indicated Ab via the IV route. Each data point represents the mean +/− SEM of the values from all 8 animals per group. (C) Plasma viral loads in rhesus macaques (n = 8 per group) challenged with a mixture of SHIV BaLP4 and SHIV 325c, 5 days after IV administration of either VRC01, PGDM1400 or VRC01/PGDM1400-10E8v4. (Figure from Xu et al., (50)).

The VRC, NIAID, and NIH evaluated the in vivo PK parameters of PGDM1400LS in human FcRn transgenic mice at a dose of 5 mg/kg via the IV route. The levels of Ab in the sera of these animals at various timepoints after administration were then quantified by using a HIV-1 trimer based ELISA (see Figure 4-21).

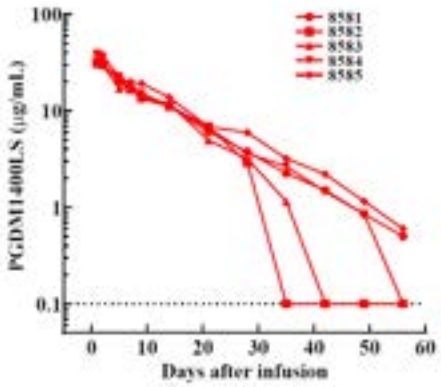

Figure 4-21 Sera levels of PGDM1400LS Ab in 5 human FcRn transgenic mice administered at 5 mg/kg via the IV route.

The PK parameters were calculated using a noncompartment model in WinNonLin software package and are summarized in Table 4-7. PGDM1400LS displayed a PK profile similar to other anti-HIV-1 Abs in this animal model and the data provide support for the development of PGDM1400LS for clinical studies.

Table 4-7 In vivo PK parameters for PGDM1400LS in human FcRn transgenic mice administered at 5 mg/kg via the IV route.

Antibody	Animal ID	Half-life Day	AUC Day*µg/mL	Clearance mL/Day/kg
PGDM1400LS	8581	9.4	417	12.0
	8582	7.7	382	13.0
	8583	6.5	371	13.5
	8584	9.3	454	10.9
	8585	8.5	523	9.6
	Average	***8.3***	***429***	***11.8***
	Standard error	***0.5***	***25***	***0.6***

4.3.3.2 Binding affinity study of PGDM1400LS compared to parental PGDM1400

The VRC, NIAID, and NIH compared the binding affinity of PGDM1400LS and PGDM1400. HIV Env Trimer 4571 binding to PGDM1400LS and the parental Ab PGDM1400 was measured by biolayer interferometry on a ForteBio OctetRED384. The binding affinity was measured and the equilibrium dissociation constant values were comparable (see Table 4-8)

Table 4-8 Binding Affinity of PGDM1400LS and PGDM1400 to HIV Env Trimer 4571

Ab	K_D (nM) ± standard error of the mean
PGDM1400LS	4.6 ± 0.9
PGDM1400	4.6 ± 0.8, 5.2 ± 0.6

4.3.3.3 In vitro neutralization study comparing PGDM1400LS with parental PGDM1400

The VRC, NIAID, and NIH compared the in vitro neutralization activities of PGDM1400LS and PGDM1400 against a multiclade virus panel (n = 3). The IC80 for PGDM1400LS and PGDM1400 were comparable (see Table 4-9). For additional in vitro neutralization data for PGDM1400 LS, please see the IB.

Table 4-9 Neutralization potency of PGDM1400LS and parental PGDM1400 in a 3-pseudovirus panel assay

Virus	Clade	IC80 (mcg/mL)		
		PGDM1400LS (production run 5537)	PGDM1400LS (production run 5515)	PGDM1400
MI369.A5	A	27.25	25.46	25.00
DU156.12	C	17.37	16.54	16.00
A03349MI.vrc4a	D	428.47	238.65	320.00

4.3.3.4 Autoreactivity evaluation of PGDM1400LS

The VRC, NIAID, and NIH assessed potential reactivity to HEp-2 cells and to phospholipid cardiolipin. The reactivity to HEp-2 cells was assessed by immunofluorescence staining (see Figure 4-22) and potential binding to cardiolipin by ELISA (see Figure 4-23). 4E10 and VRC01LS bnAbs were used as positive and negative controls, respectively. The results showed that PGDM1400LS did not display detectable binding to either HEp-2 cells or cardiolipin, suggesting that PGDM1400LS does not exhibit detectable polyspecific autoreactivity.

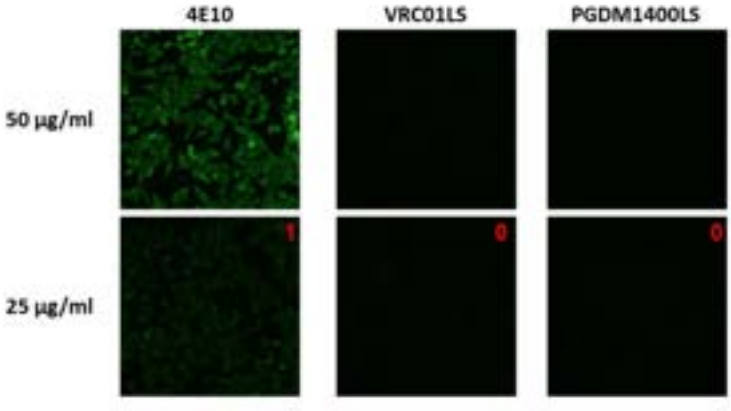

Figure 4-22 Representative images for the reactivity of 4E10, VRC01LS and PGDM1400LS to HEp-2 cells by immunofluorescence staining using 25 or 50 mcg/mL of Ab. The tests on 2 separate days showed same results, thus only 1 was shown. Reactivity scores are shown as red inset numbers.

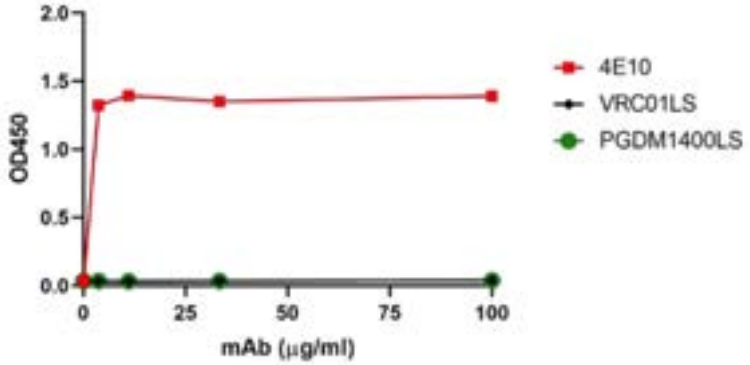

Figure 4-23 Ab binding to cardiolipin by ELISA. 4E10, VRC01LS and PGDM1400LS were tested at 100, 33.3, 11.1 and 3.7 mcg/mL and plotted with red squares, black diamonds, and green dots, respectively.

4.4 Clinical trials of PGT121, PGT121.414LS, PGDM1400, PGDM1400LS, VRC01, VRC01LS, and VRC01.23LS alone and in combinations

Table 4-10 Summary of clinical studies

Study number / status	Abs	Population(s)	Routes	ClinicalTrials .gov #	Protocol section
IAVI T001, completed	PGT121 first-in-human (FIH)	HIV- HIV+ on ART HIV+ off ART	IV, SC	NCT02960581	4.4.1
IAVI T002, completed	PGDM1400 FIH, PGDM1400+PGT121, PGDM1400 + PGT121 + VRC07-523LS HIV+ off ART	HIV- HIV+ off ART	IV	NCT03205917	4.4.2
IAVI T003, completed	PGT121 + VRC07-523LS, PGT121 + VRC07-523LS + PGDM1400, PGT121 + VRC07-523LS + PGDM1400 in HIV+ on ART	HIV- HIV+ on ART	IV	NCT03721510	4.4.3
HVTN 130/HPTN 089, completed	PGT121 + VRC07-523LS, PGDM1400 + VRC07-523LS, 10-1074 + VRC07-523LS, PGDM1400 + PGT121 + VRC07-523LS	HIV-	IV	NCT03928821	4.4.4
HVTN 136/HPTN 092, completed	PGT121.414LS FIH, PGT121.414LS + VRC07-523LS	HIV-	IV, SC	NCT04212091	4.4.5
VRC 601, completed	VRC01, FIH	HIV+ off ART	IV, SC	NCT01950325	4.4.7.1
VRC 602, completed	VRC01	HIV-	IV, SC	NCT01993706	4.4.7.1
HVTN 104, completed	VRC01	HIV-	IV, SC	NCT02165267	4.4.7.1
HVTN 703/HPTN 081, completed	VRC01	HIV-	IV	NCT02568215	4.4.7.1
HVTN 704/HPTN 085, completed	VRC01	HIV-	IV	NCT02716675	4.4.7.1
VRC 606, completed	VRC01, VRC01LS FIH	HIV-	IV, SC	NCT02599896	4.4.7.1
HVTN 116, completed	VRC01, VRC01LS	HIV-	IV	NCT02797171	4.4.7.1
VRC 607, completed	VRC01LS, VRC07.523LS	HIV+ off ART	IV	NCT02840474	4.4.7.1
HVTN 140/HPTN 101, ongoing	PGDM1400LS FIH, PGDM1400LS +VRC07-523LS+ PGT121.414.LS	HIV-	IV, SC	NCT05184452	4.4.6
VRC 615, ongoing	VRC01.23LS, FIH	HIV-	IV, SC	NCT05627258	4.4.7

4.4.1 IAVI T001

IAVI T001 is a phase 1, randomized, placebo-controlled clinical trial of the safety, PK, and antiviral activity of PGT121 in adults with HIV and adults without HIV. The study design is shown below in Table 4-11.

Table 4-11 IAVI T001 study schema

	Group	Participants	Sub-Group	Regimen	N	Dose (mg/kg) - administration
Part 1[1]	1[3]	HIV-uninfected participants	1A	PGT121/Placebo	4/1 (6/2 if DLT[2])	3 IV
			1B	PGT121/Placebo	4/1 (6/2 if DLT)	10 IV
			1C	PGT121/Placebo	4/1 (6/2 if DLT)	30 IV
			1D	PGT121/Placebo	4/1 (6/2 if DLT)	3 SC
	2[3]	HIV-infected on ART, (<50 cp/ml)	2A	PGT121/Placebo	4/1 (6/2 if DLT[2])	3 IV
			2B	PGT121/Placebo	4/1 (6/2 if DLT)	10 IV
			2C	PGT121/Placebo	4/1 (6/2 if DLT)	30 IV
Safety Monitoring Committee Review[4]						
Part 2	3[5]	HIV-infected off ART (VL $2x10^3$ – $1x10^5$cp/ml)	3A	PGT121	6 (max 9)	30 IV
		HIV-Infected off ART (VL $1x10^2$ – $2x10^3$ cp/ml)	3D[6]	PGT121	6	30 IV

DLT, dose limiting toxicity; ART, antiretroviral therapy; cp, copies; ml, milliliter
Administration of PGT 121 will be by intravenous infusion (IV) or subcutaneous injection (SC)

The trial evaluated a single IV administration of PGT121 in adults with HIV and adults without HIV. Up to 3 escalating doses were tested: 3 mg/kg, 10 mg/kg, and 30 mg/kg. Additionally, a single SC administration of PGT121 in adults who were in overall good health was tested at 3 mg/kg. A total of 48 volunteers were enrolled into the following dose subgroups:

- 1A (HIV negative, 3 mg/kg IV, n = 5),
- 1B (HIV negative, 10 mg/kg IV, n = 5),
- 1C (HIV negative, 30 mg/kg IV, n = 5),
- 1D (HIV negative, 3 mg/kg SC, n = 5);
- 2A (HIV positive on ART, 3 mg/kg IV, n = 5),
- 2B (HIV positive on ART, 10 mg/kg IV, n = 5),
- 2C (HIV positive on ART, 30 mg/kg IV, n = 5);

- 3A (HIV positive not on ART, plasma HIV-RNA between 2,000 and 100,000 copies/mL, 30 mg/kg IV, n = 9), and
- 3B (HIV positive not on ART, plasma HIV-RNA between 100 and 2,000 copies/mL, 30 mg/kg IV, n = 4).

The most common systemic reactogenicity events reported based on the percentage of participants exhibiting the event across all groups were: headache 10/48 (20.8%), malaise 5/48 (10.4%), chills 4/48 (8.3%), nausea 1/48 (2%), arthralgia 1/48 (2%), and fever 1/48 (2%). The majority were mild (Grade 1); moderate (Grade 2) systemic reactions were reported for headache 4/48 (8.3%), malaise 2/48 (4.1%), nausea 1/48 (2%), and fever 1/48 (2%). No severe (Grade 3) events were reported during the study.

The most common local reactogenicity events reported based on the percentage of participants exhibiting the event across all groups were: tenderness 14/48 (29.1%), pain 7/48 (14.5%), erythema/skin discoloration 2/48 (4.1%) and swelling/hardening 2/48 (4.1%). Most were mild (Grade 1); moderate (Grade 2) local reactions were reported for pain 1/48 (2%), tenderness 1/48 (2%) and erythema/skin discoloration 1/48 (2%). No severe (Grade 3) events were reported during the study.

Unsolicited adverse events (AEs) were AEs reported in addition to the solicited reactogenicity events. A total of 39 unsolicited AEs were reported during the study, 34 non-serious AEs in 21/48 (43.7%) participants who received investigational product and 5 non-serious AEs in participants who received placebo. The most common AEs reported based on percentage of participants exhibiting the event across all groups were: fatigue 4/48 (8.3%), headache 2/48 (4.1%), nasal congestion 2/48 (4.1%), upper respiratory tract infection 2/48 (4.1%), vessel puncture site bruising 2/48 (4.1%) and viral infection 2/48 (4.1%).

The majority were Grade 1 or 2 (mild or moderate), with one Grade 3 tonsillitis that was judged unrelated to study product. No AEs were assessed as probably or definitely related to the study product. Two Grade 1 AEs (headache and fatigue) and two Grade 2 AEs (fatigue and gastroenteritis) were assessed as possibly related to study product.

One serious adverse event (SAE), a case of pre-patellar bursitis occurring 2 months after administration of study product, was assessed as not related. No deaths, potential immune mediating disease, or HIV diagnoses were reported during the study. One pregnancy occurred during the study in participant living with HIV. The pregnancy was considered unremarkable and an infant in overall good health was delivered via caesarian section at 36-weeks gestation.

The PGT121 elimination half-life in groups without HIV was 15.5 to 28.8 days and, in groups with HIV, was 8.2 to 28.9 days. The median AUC estimates from the groups without HIV were larger than the median AUC estimates from comparable groups with HIV (ie, 3 mg/kg HIV negative vs. 3 mg/kg HIV

positive, etc). In general, the median maximum concentration (Cmax) estimates from groups without HIV were similar to the median Cmax estimates from comparable groups with HIV.

4.4.2 IAVI T002

T002 is a phase 1, randomized, placebo-controlled clinical trial of the safety, PK, and antiviral activity of PGDM1400 alone or in combination with PGT121 in adults who do not have HIV, and in combination with PGT121 and VRC07-523LS in adults living with HIV. The study design is shown in Table 4-12.

Table 4-12 IAVI T002 study schema

Participants	Group	Sub-Group	Regimen	N (Active/Placebo)	Dose (mg/kg)
HIV-uninfected participants	1	1A	PGDM1400 or Placebo	3/1	3 IV
		1B	PGDM1400 or Placebo	3/1	10 IV
		1C	PGDM1400 or Placebo	3/1	30 IV
	2	2A	PGDM1400 + PGT121 or Placebo	3/1	3 + 3 IV
		2B	PGDM1400 + PGT121 or Placebo	3/1	10 + 10 IV
		2C	PGDM1400 + PGT121 or Placebo	3/1	30 + 30 IV
HIV-infected off ART	3	3A	PGDM1400 + PGT121 + VRC07-523LS	4	20 + 20 + 20 IV
		3B	PGDM1400 + PGT121	1	30 + 30 IV

As of January 2021, the study is completed and closed. A total of 29 individuals were enrolled, including 12 participants in group 1, 12 participants in group 2, and 4 participants in group 3. In groups 1 and 2, the maximum tolerated dose (MTD) of 30 mg/kg for both products was confirmed. Overall, study product administration was safe and well-tolerated. Only grade 1 local reactogenicity was reported. Grade 1 and 2 systemic reactogenicity events included headache, myalgia, malaise and arthralgia. No Grade 3 or Grade 4 systemic symptoms were reported during the study. No AEs were assessed as probably or definitely related to the study product. No deaths, SAEs or potential immune-mediated disease AEs were reported during the conduct of the study.

Furthermore, the triple combination was well-tolerated, and no grade 3, grade 4 or SAEs and no treatment-related laboratory changes were observed during 56 days of follow-up for each group (52).

PGDM1400 concentrations have been measured in Groups 1A, 1B, and 1C (HIV negative; 3, 10, and 30 mg/kg IV, respectively) and in Groups 2A, 2B and 2C (HIV negative; 3, 10, and 30 mg/kg IV of each Ab, PGDM1400 and PGT121, respectively) by validated anti-idiotype binding antibody multiplex assay (BAMA)–based PK assays through day 168 postinfusion (Figure 4-24). Among

participants who do not have HIV, the median (min, max) PGDM1400 elimination half-life estimate was 19.4 (15.3, 24.7) days, the population-level estimate of CL was 0.191 (95% confidence interval [CI]: 0.177, 0.206) L/day, the median (min, max) volume of distribution (Vd) was 5.67 (3.42, 8.04) L, and the median (min, max) dose- and weight-adjusted AUC was 371.74 (263.76, 507.73) day/L/Kg. There were no statistically significant differences in these parameters by PGDM1400 administration alone versus coadministration with PGT121 (Group 1 vs. Group 2).

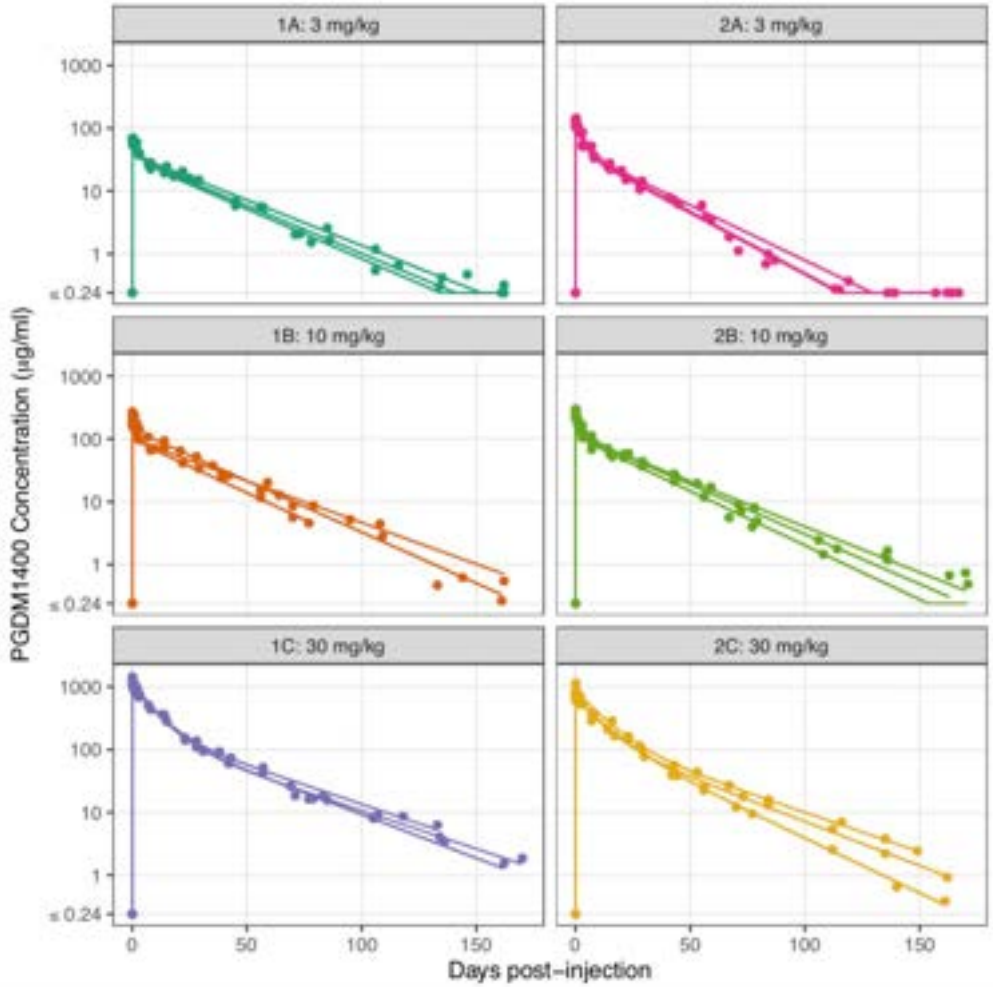

Figure 4-24 PGDM1400 binding Ab concentrations in Group 1A, 1B, and 1C (HIV negative; 3, 10, and 30 mg/kg of PGDM1400) and in Group 2A, 2B, and 2C (HIV negative; 3, 10, and 30 mg/kg of PGDM1400 and PGT121 each).

4.4.3 IAVI T003

IAVI T003 is a phase 1/2a, open-label clinical trial of the safety, tolerability, PK, and antiviral activity of PGT121, VRC07-523LS and PGDM1400 in adults who do not have HIV and in adults living with HIV. The study design is shown below in Table 4-13.

Table 4-13 IAVI T003 study schema

Group	Volunteer	Subgroup	Regimen	N	Dose (mg/kg)	Frequency	ATI
1	HIV-uninfected	1A	PGT121 +VRC07-523LS	3	30 + 30 IV	x1 (Day 0)	N/A
		PSRT review					
		1B	PGT121 +VRC07-523LS + PGDM1400	3	20 + 20 + 20 IV	x1 (Day 0)	N/A
SMC review							
2	HIV-infected on ART (VL <50 copies/mL)		PGT121 +VRC07-523LS + PGDM1400	12	20 + 20 + 20 IV	x3 (Days 0, 28, 56) Optional: additional x3 (Days 84, 112, 140)	Yes
Total				**18**			

Notes: ATI: analytical treatment interruption (starting on day 2 after participants complete their full course of ART for day 1 and after first IV infusion on day 1)

As of May 2, 2022, the study is completed and closed. A total of 19 individuals were enrolled, including 3 participants in Group 1A, 3 participants in Group 1B, and 13 participants in Group 2.

Overall, study-product administrations have been well tolerated, with no reported SAEs or potential immune-mediated disease. No safety-related study pauses have occurred. The most common Grade 1 or greater systemic reactogenicity events reported across all Groups, based on the percentage of volunteers exhibiting the event, were malaise and headache, reported in 33.3% and 27.8% of volunteers, respectively. One participant in Group 2 reported severe reactogenicity of malaise and headache after the third infusion, which lasted less than two days. No severe (Grade 3 or greater) AE related to the study product have been reported. Systemic reactogenicity events reported by Group 1A participants included mild nausea, moderate malaise, and moderate headache. In Group 1B, mild malaise and mild headache were reported.

As an overall safety conclusion, safety data for administration of the 2-mAb combination IP (PGT121 and VRC07-523LS) and 3-mAb combination IP (PGT121, VRC07-523LS and PGDM1400) investigated in this study demonstrate acceptable safety profiles.

4.4.4 HVTN 130/HPTN 089

HVTN 130/HPTN 089 is a randomized, phase 1 clinical trial in healthy adults without HIV to evaluate the safety, tolerability, and serum concentrations of PGT121, PGDM1400 and 10-1074, when a single dose of each is administered IV before a single dose of VRC07523LS, and when PDGM1400 and PGT121 are administered sequentially IV before VRC07-523LS for 2 doses, 4 months apart(Table 4-14). The first participant was enrolled in the study on July 31, 2019. The final infusion was administered on March 9, 2020.

Table 4-14 HVTN 130/HPTN 089 (Version 1.0) study schema

Study arm	N	Dose	Route	M0[1]	M4
Group 1	6	20+20 mg/kg	IV	PGT121 VRC07-523LS	—
Group 2	6	20+20 mg/kg	IV	PGDM1400 VRC07-523LS	—
Group 3	6	20+20 mg/kg	IV	10-1074 VRC07-523LS	—
Group 4[2]	9	20+20+20 mg/kg	IV	PGDM1400 PGT121 VRC07-523LS	PGDM1400 PGT121 VRC07-523LS
Total	27				

[1] The mAbs are infused sequentially in the order shown.
[2] Opening enrollment in Group 4 follows review of safety data for all participants in Groups 1-3.

A total of 33 administrations of PGT121, VRC07-523LS, 10-1074 and PGDM1400 occurred during the study. Overall, IV administration of study products in HVTN 130/HPTN 089 was generally well tolerated.

As of December 2020, no grade 3 or higher infusion-site erythema or induration were reported; no grade 3 AEs deemed related to PGT121, PGDM1400, 10-1074 or VRC07 523LS were reported; and no related SAEs have been reported. Two participants developed unsolicited AEs that were assessed as related to the study products, which resolved without residual effects. One participant in Group 3 developed a related AE of mild paresthesia with each infusion ("pins and needles" bilaterally in hands lasting a few minutes each time) which resolved the following day. One participant in group 2 developed mild infusion-related reactions (chills, mild upper back muscle pain, mild joint pain in wrists, and a mild headache) after both study-product infusions were complete, which resolved in 1 hour.

Solicited AEs were reported as mild to moderate in severity and included pain or tenderness, induration, malaise and/or fatigue, myalgias, arthralgias, chills, headache, nausea, and facial flushing. There were no study pauses due to safety concerns or discontinuation of study products due to AEs.

4.4.5 HVTN 136/HPTN 092

HVTN 136/HPTN 092 is the first clinical study of the PGT121.414.LS mAb. This phase 1, dose-escalation, open-label clinical trial is aiming to examine the safety, tolerability, dose, and PK of PGT121.414.LS with and without VRC07-523LS, a CD4bs mAb (see Table 4-15). The hypothesis is that PGT121.414.LS alone and paired with VRC07-523LS will be safe for administration to adults who do not have HIV and are in overall good health by both the IV and SC routes. The first participant was enrolled in the study on November 10, 2020. The final infusion was administered on May 3, 2022.

A total of 9 participants received PGT121.414.LS alone via IV and 10 participants received PGT121.414.LS along with VRC07-523LS via IV. In Part A of the study, PGT121.414.LS was administered via IV infusion at 3, 10, or 30 mg/kg (Groups 1-3) or via SC infusion at 5 mg/kg (Group 4). Each group in Part A had 3 participants. In Part B of the study, participants received consecutive administrations of PGT121.414.LS followed by VRC07-523LS, at 20 mg/kg IV each per dose (Group 5) or 5 mg/kg SC each per dose (Group 6) at 3 infusion visits. Each group in Part B had 10 participants, yielding a total sample size for Parts A and B of 32, out of which 19 participants received IV infusions and 13 participants received SC infusions (see Table 4-15). Participants were followed for 32 weeks after the last study-product administration via IV infusion and 24 weeks after the last study-product administration via SC infusion.

Table 4-15 HVTN 136/HPTN 092 schema

Study arm	Number	Dose	Route	Month 0 (Day 1)	Month 4 (Day 112)	Month 8 (Day 224)
Part A						
Group 1*	3	3 mg/kg	IV	PGT121.414.LS	—	—
Group 2[a*]	3	10 mg/kg	IV	PGT121.414.LS	—	—
Group 3[b*]	3	30 mg/kg	IV	PGT121.414.LS	—	—
Group 4[b*]	3	5 mg/kg	SC	PGT121.414.LS	—	—
Part B						
Group 5[c]	10	20 mg/kg + 20 mg/kg	IV	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS
Group 6[c]	10	5 mg/kg + 5 mg/kg	SC	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS
Total	32					

[a] Enrollment in Group 2 begins following review of safety data for participants in Group 1.

[b] Enrollment in Groups 3 and 4 begins concurrently following review of safety data for participants in Groups 1 and 2.

[c] Enrollment in Groups 5 and 6 begins concurrently following review of safety data for participants in Part A. Details described in Section 11.3

*Additional participants may be enrolled to ensure the availability of 2-week safety data from at least 3 participants

No Grade 3 or higher infusion site erythema or induration was reported; no Grade 3 SAEs deemed related were reported.

Overall, product administrations were generally well tolerated. In the IV administration groups, solicited AEs reported as mild to moderate in severity included pain or tenderness, malaise/fatigue, chills, headache, arthralgia, myalgia, nausea, and unexplained diaphoresis. There were six grade 1 (mild) infusion-related reactions in 3 participants in Group 5, all of whom received 20 mg/kg PGT121.414.LS + VRC07-523LS IV infusions. All infusion-related reactions occurred after completion of both product infusions. These infusion reactions were characterized by chills, fatigue/malaise, muscle aches, nausea with vomiting, and headache, all of which spontaneously resolved after about 15 minutes. Two infusion-related reactions occurred in a participant in whom the first reaction was characterized by nausea, vomiting, fatigue/malaise, and headache (which resolved in about 15 minutes), as well as arthralgia. All symptoms resolved within a hour. No participant required epinephrine or steroids.

All 6 of the related unsolicited AEs in the IV groups are the same infusion-related reactions detailed above; no additional related unsolicited AEs were reported.

4.4.6 HVTN 140/HPTN 101

HVTN 140/HPTN 101 is a phase 1, dose-escalation, open-label clinical trial aiming to examine the safety, tolerability, dose, and PK of PGDM1400LS with and without VRC07-523LS and PGT121.414.LS. The hypothesis is that PGDM1400LS alone and coadministered with VRC07-523LS and PGT121.414.LS will be safe for administration by both the IV and SC routes to adults who do not have HIV and are in overall good health.

A total of 9 participants received PDGM1400LS alone, via IV and 48 participants received PDGM1400LS in combination with other mAbs, via IV. In Part A, PGDM1400LS was administered via IV infusion at 5, 20, or 40 mg/kg (Groups 1, 2 and 4) or via SC infusion at 20 mg/kg (Group 3) and 40 mg/kg (Group 5) to 3 participants in each group for 1 infusion visit. In Part B participants received consecutive administrations of PGDM1400LS and VRC07-523LS, followed by PGT121.414.LS, at 20 mg/kg or 1.4g each per the IV or SC route, or 40 mg/kg via the IV route only. Participants will be followed for 24 weeks after the last study-product administration via IV infusion in Part A, and for 32 weeks after the last study-product administration in Part B.

A total of 15 administrations (9 IV infusions and 6 SC infusions) of PGDM1400LS in Part A and 160 administrations (96 IV infusions and 64 SC infusions) of PGDM1400LS with VRC07-523LS and PGT121.414.LS in Part B have occurred.

As of January 2023, data cleaning is ongoing. In the IV administration groups, no SAEs have been reported and no study pauses due to safety concerns have occurred. No Grade 3 or higher infusion-site erythema or induration were reported. Solicited AEs deemed related to study product reported as mild to moderate in severity included the following: infusion-site erythema, induration, pain or tenderness, fever, malaise/fatigue, headache, myalgia, arthraligia, chills,

nausea, and unexplained diaphoresis. One infusion-related reaction was reported in Group 6, which was characterized by diaphoresis, pre-syncope (lightheadedness, muscular weakness, blurred vision, and feeling faint, but not fainting), chills, muscle aches, nausea, blurry or narrowed vision, transient ear ringing (while feeling lightheaded), and fatigue/malaise (treated with 25-mg PO benedryl once). All symptoms fully resolved within 2 days. No other related AEs have been reported in any of the IV infusion administration groups.

Table 4-16 HVTN 140/HPTN 101 schema

Study arm	N*	Dose	Route	Month 0	Month 4
Part A					
Group 1	3	5 mg/kg	IV	PGDM1400LS	-
Group 2[1]	3	20 mg/kg	IV	PGDM1400LS	-
Group 3[1]	3	20 mg/kg	SC	PGDM1400LS	-
Group 4[2]	3	40 mg/kg	IV	PGDM1400LS	-
Group 5[2]	3	40 mg/kg	SC	PGDM1400LS	-
Part B**					
Group 6[3]	16	20 mg/kg + 20 mg/kg + 20 mg/kg	IV	PGDM1400LS + VRC07-523LS + PGT121.414.LS	PGDM1400LS + VRC07-523LS + PGT121.414.LS
Group 7[3]	16	20 mg/kg + 20 mg/kg + 20 mg/kg	SC	PGDM1400LS + VRC07-523LS + PGT121.414.LS	PGDM1400LS + VRC07-523LS + PGT121.414.LS
Group 8[3]	16	1.4 g + 1.4 g + 1.4 g	IV	PGDM1400LS + VRC07-523LS + PGT121.414.LS	PGDM1400LS + VRC07-523LS + PGT121.414.LS
Group 9[3]	16	1.4 g + 1.4 g + 1.4 g	SC	PGDM1400LS + VRC07-523LS + PGT121.414.LS	PGDM1400LS + VRC07-523LS + PGT121.414.LS
Group 10[4]	16	40 mg/kg + 40 mg/kg + 40 mg/kg	IV	PGDM1400LS + VRC07-523LS + PGT121.414.LS	PGDM1400LS + VRC07-523LS + PGT121.414.LS
Total	95				

* Additional participants may be enrolled to ensure the availability of safety data from at least 3 participants in each group

[1] Opening enrollment in Groups 2 and 3 follows review of safety data for participants in Group 1. Details are described in Section 11.3.1.

[2] Opening enrollment in Group 4 and 5 follows review of safety data for participants in Groups 1-3

** Abs will be administered sequentially as 3 separate infusions

[3] Opening enrollment in Groups 6, 7, 8, and 9 follows review of safety data for participants in Part A.

[4] Opening enrollment in Group 10 follows review of safety data for participants from Groups 1-9.

4.4.7 VRC 615

The VRC615 is a first-in-human (FIH), phase 1, open-label, dose-escalation study of the safety and PK of a human mAb, VRC-HIVMAB0115-00-AB (VRC01.23LS), administered IV or SC to adults in overall good health.

This open-label study will evaluate VRC01.23LS (VRC-HIVMAB0115-00-AB) in a dose-escalation design to examine safety, tolerability, dose, and PK in adults who are in overall good health (seeTable 4-17). The primary hypothesis is that SC and IV administrations of VRC01.23LS will be safe and well-tolerated in adults who are in overall good health. A secondary hypothesis is that VRC01.23LS will be detectable in human sera with a definable half-life. The study opened in December 2022 and results are expected to be available by the end of 2023.

Table 4-17 VRC 615 schema

Group	N	VRC01.23LS dose and route	Dosing schedule		
			Day 1	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		X
5	5	5 mg/kg SC	X	X	
6	5	20 mg/kg IV	X	X	X
Total	22*	* Enrollment up to a total of 40 participants is permitted if additional participants are necessary for safety or PK evaluations.			

4.4.7.1 Parental VRC01, VRC01LS Safety in Clinical Trials

VRC01LS, a parental mAb of VRC01.23LS, differs from its antecedent, VRC01, by the 2 amino acid mutations, LS, that increase binding to FcRn and extend mAb in vivo half-life. The 2 mAbs are otherwise identical in sequence.

VRC01

VRC01, the original VRC broadly neutralizing HIV-1 CD4bs mAb isolated from a participant, has been clinically evaluated in 15 trials, including phase 1 studies VRC 601 (NCT01950325), VRC 602 (NCT01993706), and HVTN 104 (NCT02165267) and phase 2 studies HVTN 704/HPTN 085(NCT02716675) and HVTN 703/HPTN 081 (NCT02568215).

As of March 2019, VRC01 has been administered either IV or SC at doses up to 40 mg/kg to over 3,260 HIV-seronegative adults in overall good health, 110 adults living with HIV, 39 infants who have been exposed to HIV-1, and 6 infants with HIV. As of April 2022, there have been no SAEs related to VRC01, as assessed by the Sponsor. This experience includes the results of two phase 2 AMP trials (53).

To date, the clinical trial safety experience with VRC01-class mAbs has been reassuring. In HVTN 104, IV administration of VRC01 was generally well-tolerated with mild pain and/or tenderness commonly reported at the site of the IV infusion. Mild-to-moderate systemic reactogenicity symptoms were reported by VRC01 recipients following at least 1 of the infusions, but there was no clear relationship with frequency or severity to the dose of VRC01 (54). No hypersensitivity reactions or cytokine release syndrome symptoms were reported in HVTN 104 (54).

The efficacy trials HVTN 704/HPTN 085 and HVTN 703/HPTN 081 have accumulated significant additional VRC01 clinical experience. More than 40,000 infusions of 10 mg/kg and 30 mg/kg VRC01 have been given to more than 3000 adults without HIV across both trials. While final safety analysis is ongoing, the safety profile is reassuring, thus far. In the combined trials, 40642 IV infusions were administered and 209 AEs deemed related to study product were reported. The mean and median onset of these AEs was day 1, the day of infusion. Of these AEs deemed related to study product, all ≥ grade 3 AEs (7 grade 3 AEs and 1 grade 4 AE) and 95% of AEs of any grade were reported within 3 days postinfusion. VRC01 was well-tolerated, with low rates of infusion-related reactions (IRRs): 1.7% of participants in HVTN 704/HPTN 085 and 4.8% of participants in HVTN 703/HPTN 081 experienced IRRs to VRC01/placebo. In the combined trials, 132 out of 160 IRRs developed in VRC01 recipients. IRRs were typically mild or moderate (96.2% were deemed mild or moderate and 3.8% were deemed severe), successfully managed at the CRS, and resolved without sequelae.

VRC01LS

VRC HIV-1 human bnAb VRC01LS, the parent of VRC01.23LS, has been evaluated in 5 clinical trials.A total of, 112 participants have received 1 or more doses of VRC01LS. VRC01LS IV and SC administrations have been well-tolerated in adults and children; there have been no SAEs related to VRC01LS. Clinical information regarding VRC01LS is available under DAIDS investigational new drug (IND) 125494 (VRC 606, HVTN 116), DAIDS IND 140909 (dual bnAb protocol), DAIDS IND 130804 (VRC 607), and in Gaudinski et al (51).

In the 3 prevention studies (VRC 606, HVTN 116, and P1112), 56 adults in overall good health and 21 infants who have been exposed to HIV-1 received VRC01LS in doses ranging from 5 to 40 mg/kg IV and 5 mg/kg SC in adults and up to 100 mg/dose SC in infants. VRC 606, a VRC01LS phase 1, dose-escalation study, has been completed and results published (51) (NCT02599896). HVTN 116, a phase 1 study to evaluate VRC01LS and VRC01 safety, tolerability, PK, and antiviral activity in adults who are in overall good health, has also been completed (NCT02797171). A phase 1 study, IMPAACT P1112, evaluating the safety and PK of VRC01, VRC01LS, or another CD4bs mAb, VRC07-523LS, in infants who have been exposed to HIV-1, has completed IP administration (NCT02256631).

In the 2 therapeutic studies in individuals living with HIV (VRC 607 and dual bnAb treatment in children), 7 viremic adults living with HIV and 28 virally suppressed children with HIV received VRC01LS at doses ranging from 10 to 40 mg/kg IV. VRC 607/A5378, a phase 1, single-dose study evaluating the safety and antiviral effect of VRC01LS and VRC07-523LS in viremic adults living with HIV, has been completed (NCT02840474). VRC01LS continues to be studied in virally suppressed children with HIV in a phase 1/2 study (dual bnAb), administering VRC01LS and mAb 10-1074 (NCT03707977). Collectively, safety data from these studies indicate that VRC01LS is safe and well tolerated at doses ranging from 5 mg/kg to 40 mg/kg. The overall safety profile is consistent with expected events for mAbs, most commonly mild to moderate reactogenicity, which occurs shortly after product administration and is self-limited. There have been no unexpected safety trends identified and no SAEs related to VRC01LS.

4.5 Potential risks of study products and administration

Risk type	Risk frequency	Summary
General risks		
mAbs	General risks, typically mild	• Fever, flushing, chills, rigors, nausea, vomiting, diarrhea, pain, headache, dizziness • Pruritus, rash, urticaria, angioedema • Shortness of breath, bronchospasm, tachycardia, hypotension, hypertension, chest pain
	Rare	• Delayed allergic reactions may occur approximately 24 hours after administration, though can occur several days to a few weeks after administration, and can include serum sickness, which is characterized by urticaria, fever, lymphadenopathy, anaphylaxis and arthralgia. This reaction is more likely to occur with chimeric Abs, and has not been observed with fully human mAbs. • Reactions related to the rate of infusion have been described for several FDA-licensed mAbs. These mAb-related events typically occur within the first 24 hours of administration, though have not been observed with anti-HIV mAbs to date. Cytokine release syndrome typically occurs within the first few hours of administration, and usually with the first administration when the largest number of target cells expressing antigen are present. Cytokine release syndrome can be effectively managed by temporarily holding the administration, administering anti-histamines, and restarting the IV infusion at a slower rate (55).

Risk type	Risk frequency	Summary
	Theoretical	• Additional reactions, such as tumor lysis syndrome and cytokine release syndrome, have been previously described with chimeric and humanized Abs, usually with mAbs targeting human antigens. Cytokine release syndrome has been described with human mAbs targeting lymphocyte cell-surface antigens. Serious allergic reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia, are rare and often associated with mAbs targeting human proteins or with nonhuman mAbs. • Thrombocytopenia, autoimmune diseases, cancer, dermatitis, and cardiotoxicity (56).
mAb-Associated Reactivity	Possible	• There is a possibility that receipt of the study products will cause a reactive result on some currently available HIV test kits, especially if testing occurs close to study-product administration timepoints (see Section 9.5.1).
Risks associated with study products		
VRC01.23LS		• Safety data expected from VRC615 by the end of 2023 (see Section 4.4.7). However, multiple studies using parental Abs to VRC01.23LS have reported no local or systemic solicited AEs and no unsolicited AEs. Product administrations have been well tolerated (also see Section 4.4.7).
PGT121.414.LS		• There have been no related Grade 3 SAEs. Mild to moderate SAEs reported (see Section 4.4.5 and Section 4.4.6 for details). To date, there have been no study safety pauses for AEs and product administrations have been generally well tolerated.
PDGM1400LS		• There have been no related Grade 3 SAEs. Mild to moderate SAEs reported (see Section 4.4.5 and Section 4.4.6 for details). The majority of participants have reported no local or systemic solicited AEs and no unsolicited AEs. To date, there have been no study safety pauses for AEs. Product administrations have been well tolerated
Risks from study procedures		
Blood draw	General risks, typically mild	• Pain, bruising • Minor swelling or bleeding at the site
	Uncommon or rare	• A feeling of lightheadedness or fainting • Infection at the site where the blood is taken or anemia with large or repeated blood draws
IV infusion	General risks	• Risk of infection at the site of IV catheter insertion is mitigated by careful decontamination of skin prior to catheter placement and through the use of infection-control practices during infusion • Risk of product contamination will be minimized through the use of aseptic technique during product preparation and administration.

Risks of interference with common HIV tests:

An anti-HIV mAb is not likely to directly reduce or inhibit the assays used to detect HIV-1.

5 Objectives and endpoints

5.1 Primary objectives and endpoints

Primary objective 1:

To evaluate the safety and tolerability of VRC01.23LS when administered alone via IV route (Part A) and of VRC01.23LS + PGT121.414.LS + PGDM1400LS, when administered consecutively via IV route (Part B)

Primary endpoints 1:

- Local and systemic solicited AEs, laboratory measures of safety, unsolicited AEs, and SAEs
- Early discontinuation of administration and reason(s) for discontinuation and early study termination

Primary objective 2:

To evaluate the serum concentrations and PK of VRC01.23LS when administered alone via IV (Part A) and of VRC01.23LS + PGT121.414.LS + PGDM1400LS after consecutive administration via IV route (Part B)

Primary endpoint 2:

Serum concentrations of VRC01.23LS, PGT121.414.LS, and PGDM1400LS at prespecified timepoints among participants who received all scheduled product administrations

Primary objective 3:

To evaluate the individual mAb-specific serum neutralizing activity of VRC01.23LS when administered alone via IV route (Part A) and of VRC01.23LS + PGT121.414.LS + PGDM1400LS, after consecutive administration via IV route (Part B)

Primary endpoint 3:

Magnitude of serum neutralizing activity measured with mAb-specific Env-pseudotyped viruses in TZM-bl cells at prespecified timepoints among participants who received all scheduled product administrations

5.2 Secondary objectives and endpoints

Secondary objective 1:

To correlate serum concentrations of VRC01.23LS, PGT121.414.LS, and PGDM1400LS with corresponding virus neutralization titers in serum

Secondary endpoints 1:

- Serum concentrations of VRC01.23LS, PGT121.414.LS, and PGDM1400LS at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

- Magnitude of serum neutralizing activity measured with Env-pseudotyped viruses in TZM-bl cells at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

Secondary objective 2:

To determine whether the mAbs maintain their expected combined magnitude and breadth of serum neutralizing activity after each 3-mAb administration as predicted by the known magnitude and breadth of neutralization of the corresponding mAb combinations as noninfused clinical products

Secondary endpoint 2:

Magnitude of neutralizing activity against a panel of Env-pseudotyped reference viruses in TZM-bl cells at selected timepoints for all participants in all groups regardless of how many product administrations and how much product they received

Secondary objective 3:

To determine whether ADAs are present and whether there is a correlation among VRC01.23LS, PGT121.414.LS, and PGDM1400LS concentrations and ADA titers in serum samples

Secondary endpoint 3:

Serum VRC01.23LS, PGT121.414.LS, and PGDM1400LS concentrations and ADA titers in each group measured at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

5.3 Exploratory objectives

Exploratory objective 1:

To determine whether any confirmed positive ADA samples have functional activity that impacts the neutralizing activity of VRC01.23LS, PGT121.414.LS and PGDM1400LS.

Exploratory objective 2:

To further evaluate non-neutralizing antiviral activities, additional assays (eg, antibody-dependent cell-mediated cytotoxicity [ADCC], antibody-dependent cellular phagocytosis [ADCP], virion capture, Fc receptor binding) may be performed for activities that the VRC01.23LS, PGT121.414.LS, and PGDM1400LS are shown to exhibit in vitro

Exploratory objective 3:

To conduct analyses related to predicting serum neutralization over time against a set of potentially exposing viruses in a future efficacy trial for ranking and down-selecting bnAb regimens

Exploratory objective 4:

To conduct analyses related to furthering the understanding of HIV, passive immunity, immunology, Ab mediated prevention, acceptability and clinical trial conduct.

6 Statistical considerations

6.1 Accrual and sample-size calculations

Recruitment will seek to enroll 77 adults without HIV who are in overall good health and will be conducted in the Republic of South Africa. Participants in Part A will be administered VRC01.23LS as 1 IV infusion at 5, 20, or 40 mg/kg (Groups 1-3) with n = 5 participants per group. Participants in Part B of the study will receive 2 IV infusions of 5 mg/kg each per dose (Group 4), 20 mg/kg for VRC01.23LS, 5 mg/kg for PGT.121.414.LS, and 5 mg/kg for PGDM1400LS each (Group 5), 20 mg/kg each per dose (Group 6), 40 mg/kg for VRC01.23LS, 5 mg/kg for PGT.121.414.LS, and 5 mg/kg for PGDM1400LS (Group 7), or 40 mg/kg each per dose (Group 8). Each Group in Part B will enroll n = 8 participants, except for Group 8, which will enroll 30. All groups 1-8 are open-label. To ensure that both persons assigned male sex at birth (AMAB) and AFAB persons will be adequately represented, the trial will enroll at least 40% of each.

Since enrollment is concurrent with receiving the first product administration, all participants will provide some safety data. However, we cannot rule out the possibility of missing data due to various reasons, such as early termination in study participation, problems in shipping specimens, or high assay background. Taking this into account, the sample size calculations account for 20% of enrolled participants having missing data for the primary lab endpoint at a given timepoint. To put this number into context, immunogenicity data from 17 phase 1 and from 2 phase 2a HVTN vaccine trials, which began enrolling after June 2005 (data as of September 2014), indicate that 17% is a reasonable estimate for the rate of missing data at a given timepoint. In HVTN 104 (phase 1 trial of VRC01), approximately 10-15% of mAb concentration data were missing at the primary timepoints.

6.1.1 Sample-size calculations for safety

Primary objective 1 of this study is to evaluate the safety and tolerability of infusion of VRC01.23LS alone, and consecutive IV infusions of VRC01.23LS, PGT121.414.LS, and PGDM1400LS. The goal of the safety evaluation is to identify safety concerns associated with product administration. The ability of the study to detect SAEs can be expressed by the true event rate, defined as the proportion of participants experiencing any SAE, above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. To be more specific, for each treatment group of size n = 5 in Part A, there is a 90% or more chance of observing at least 1 event if the true rate of such an event is 36.9% or more, and there is a 90% or more chance of observing no events if the true rate is 2.1% or less. For IV infusion Groups 1-3 combined with n = 15 in Part A, there is a 90% chance or more of observing at least 1 event if the true rate is 14.2% or more, and there is a 90% chance or more of observing no events if the true rate is 0.7% or less. For each group of size n = 8 in Part B, there is a 90% or more chance of observing at least 1 event if the true

rate of such an event is 25.0% or more, and there is a 90% or more chance of observing no events if the true rate is 1.3% or less. For Group 8 in Part B with n = 30, there is a 90% or more chance of observing at least 1 event if the true rate of such an event is 7.4% or more, and there is a 90% or more chance of observing no events if the true rate is 0.4% or less. Table 6-1 summarizes the probability of observing 0 events, 1 or more events, and 2 or more events among groups of size 5 (Groups 1-3), 15 (Groups 1-3 combined), 8 (Groups 4-7), and 30 (Group 8) for various true event rates. To put these numbers into perspective, in HVTN vaccine trials from December 2000 through April 2014, about 4% of participants who received placebos experienced an SAE.

Table 6-1 Probability of observing 0 events, 1 or more events, and 2 or more events, among groups of size 5 (Groups 1-3), 15 (Groups 1-3 combined), 8 (Groups 4-7), and 30 (Group 8) for various true event rates

Group size	True event rate (%)	Pr(0/n_1)	Pr(1+/n_1)	Pr(2+/n_1)
5	1	0.95	0.05	< 0.01
	4	0.82	0.18	0.01
	10	0.59	0.41	0.08
	20	0.33	0.67	0.26
	30	0.17	0.83	0.47
15	1	0.86	0.14	< 0.01
	4	0.54	0.46	0.12
	10	0.21	0.79	0.45
	20	0.04	0.96	0.83
	30	< 0.01	> 0.99	0.96
8	1	0.92	0.08	<0.01
	4	0.72	0.28	0.04
	10	0.43	0.57	0.19
	20	0.17	0.83	0.50
	30	0.06	0.94	0.75
30	1	0.74	0.26	0.04
	4	0.29	0.71	0.34
	10	0.04	0.96	0.82
	20	< 0.01	> 0.99	0.99
	30	< 0.01	> 0.99	> 0.99

6.1.2 Sample-size calculations for serum mAb concentrations

Primary objective 2 of this study is to evaluate serum concentrations of VRC01.23LS at several timepoints (ie, PK) when administered alone and of VRC01.23LS, PGT121.414.LS, and PGDM1400LS following consecutive IV administration of these mAbs. This objective is descriptive and will be accomplished by estimating the mean serum concentration of each mAb within each treatment group at specific timepoints following each administration. The precision with which a true mean concentration can be estimated from observed data depends on the standard deviation (SD) of the measurements and the sample size. Table 6-2 summarizes two-sided 95% CIs for the mean mAb concentration

for selected values of the observed average mAb concentration and two choices of SDs (SD of log-transformed mAb concentration = 0.5 or 1.0). The construction of these CIs assumed sample sizes of n = 6 or 7 per arm in Groups 4-7 and n = 24 or 27 in Group 8 of Part B, reflecting a missingness rate of 10-20%, compared to a planned treatment group size of 8 participants in Groups 4-7 and 30 participants in Group 8. The calculations assumed that log-transformed serum concentrations are approximately normally distributed. To account for the small sample sizes, a t-distribution was used to construct CIs. For instance, with an observed mean $\log_e$ serum level of $\log_e$(10 mcg/mL) and assuming an SD of 0.5 for their log-transformed values, a two-sided 95% CI for the true mean mAb concentration level is (5.9, 16.9) (in mcg/mL) with an effective sample size of 6 participants. Of note, an SD of less than 1.0 was generally observed in the log-transformed serum concentrations of VRC01 at various timepoints post–IV infusions of VRC01 in HVTN 104 (57).

Table 6-2 Two-sided 95% CIs based on observing a particular average $\log_e$ mAb concentration in Part B participants, taking 10% or 20% attrition into consideration (n = 6/arm or 7/arm for Groups 4-7 and n = 24 or 27 for Group 8 in Part B)

Observed average $\log_e$-mAb concentration ($\log_e$ mcg/mL)	SD of $\log_e$-mAb concentration ($\log_e$ mcg/mL)	95% CI (mcg/mL) n = 6	95% CI (mcg/mL) n = 7	95% CI (mcg/mL) n = 24	95% CI (mcg/mL) n = 27
$\log_e$(1)	0.5	(0.59,1.7)	(0.63,1.6)	(0.81,1.2)	(0.82,1.2)
$\log_e$(10)		(5.9,17)	(6.3,16)	(8.1,12)	(8.2,12)
$\log_e$(50)		(30,85)	(31,79)	(40,62)	(41,61)
$\log_e$(100)		(59,169)	(63,159)	(81, 124)	(82,122)
$\log_e$(500)		(296,845)	(315,794)	(405,618)	(410,609)
$\log_e$(1000)		(592,1690)	(630,1588)	(810,1235)	(821,1219)
$\log_e$(1)	1.0	(0.35,2.9)	(0.40,2.5)	(0.66,1.5)	(0.67,1.5)
$\log_e$(10)		(3.5,29)	(4.0,25)	(6.6,15)	(6.7,15)
$\log_e$(50)		(18,143)	(20,126)	(33,76)	(34,74)
$\log_e$(100)		(35, 286)	(40,252)	(66,153)	(67,149)
$\log_e$(500)		(175,1428)	(198,1261)	(328,763)	(337,743)
$\log_e$(1000)		(350,2856)	(397,2521)	(656,1525)	(673,1485)

6.1.3 Sample-size calculations for serum neutralization activity

Primary objective 3 of this study is to evaluate serum neutralization titers of VRC01.23LS against Env-pseudotyped viruses specific to VRC01.23LS at several timepoints following IV administration of VRC01.23LS and of VRC01.23LS, PGT121.414.LS, and PGDM1400LS against Env-pseudotyped viruses specific to each mAb at several timepoints following consecutive IV administrations. This objective is also descriptive, and will be accomplished by estimating the mean serum neutralization titers of each mAb against the specific virus within each treatment group. The precision with which a true mean neutralization titer can be estimated from observed data depends on the SD of the measurements and the sample size. Table 6-3 summarizes two-sided 95% CIs for

the mean neutralization titer for selected values of the observed average infectious dose ID50 or ID80 neutralization titer. The construction of these CIs assumed sample sizes of n = 6 or n = 24, reflecting an attrition rate of 20% compared to the planned treatment group size of 8 or 30 participants in Part B, respectively. The calculations assumed that log-transformed neutralization titers are approximately normally distributed. To account for the small sample sizes, a t-distribution was used to construct CIs. For instance, with an observed mean titer of $\log_e(50)$ and assuming an SD of 0.5 for their log-transformed values, a two-sided 95% CI for the true mean neutralization titer is (29.6, 84.5) and (40.5, 61.8) with an effective sample size of 6 or 24 participants. Of note, based on neutralization data against a global panel of 11 pseudoviruses in 6 participants in HVTN 104, an SD of approximately 1.0 was observed in the log-transformed ID50 titers at various timepoints post–IV infusions of VRC01 (57).

Table 6-3 Two-sided 95% CIs based on observing a particular average $\log_e$- neutralization titer in n = 6 or n = 24 participants in 1 treatment arm, considering 20% attrition of n = 8 or n = 30 participants

Observed average $\log_e$ neutralization titer	SD of $\log_e$ neutralization titer	95% CI n = 6	95% CI n = 24
$\log_e(10)$	0.5	(5.9,17)	(8.1,12)
$\log_e(50)$		(30,85)	(40,62)
$\log_e(100)$		(59,169)	(81,124)
$\log_e(500)$		(296,845)	(405,618)
$\log_e(1000)$		(592,1690)	(810,1235)
$\log_e(10)$	1.0	(3.5,29)	(6.6,15)
$\log_e(50)$		(18,143)	(33,76)
$\log_e(100)$		(35,286)	(66,153)
$\log_e(500)$		(175,1428)	(328,763)
$\log_e(1000)$		(350,2856)	(656,1525)

6.2 Randomization

There will be no randomization for Part A. Group 1 will be enrolled first. Contingent on safety data from Group 1, Group 2 will be enrolled. Contingent on safety data from Group 2, Group 3 will be enrolled. Contingent on data from Part A, Groups 4, 5, 6, 7, and 8 will be randomized in blocks to ensure balance across groups for simultaneous enrollment. Specifically, for the first 7 blocks, participants will be allocated according to a 1:1:1:1:4 ratio; for the last block, participants will be allocated according to a 1:1:1:1:2 ratio. A participant's randomization assignment will be computer generated and provided to the CRS pharmacist through a web-based randomization system.

6.3 Blinding

Participants and CRS staff will be unblinded to participant treatment arm assignments. Laboratory Center (LC) staff will be unblinded to whether a sample is from Part A or Part B, but will remain blinded to treatment assignment within Part A or Part B during sample analysis.

6.4 Statistical analyses

This section describes the final study analyses, unblinded as to treatment arm assignment. All safety data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many study-product administrations and how much study product they received. In the rare instance that a participant receives the wrong treatment at a specific study-product administration time, the Statistical Analysis Plan (SAP) will address how to analyze the participant's safety data. Analyses of safety data are modified intent-to-treat (MITT), in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of the brief length of time between randomization and enrollment—typically no more than 4 working days—very few such individuals are expected. The primary analysis of mAb concentration and antiviral functional activity data are per-protocol (PP), in that only individuals who receive the expected mAb at the expected dose level within the expected visit window contribute data. Secondary analysis will also involve the MITT cohort, and when necessary, account for the actual specimen collection time and the actual time and dose amount of each product administration.

Analyses for primary endpoints will be performed using SAS and R. Additional software may be used to perform noncompartmental PK and population PK analyses (eg, Monolix). All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

No formal multiple-comparison adjustments will be employed for multiple primary or secondary endpoints. However, multiplicity adjustments will be made for certain primary or secondary endpoint assays, as discussed below, when the assay endpoint is viewed as a collection of hypotheses (eg, testing multiple pseudoviruses to determine a positive antiviral functional activity response). Unless otherwise noted, all statistical tests will be two-sided and will be considered statistically significant if $p < 0.05$.

6.4.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, mAb concentration, mAb functionality, and ADA for primary- and secondary-objective analyses.

6.4.2 Baseline comparability

Treatment arms will be compared for baseline participant characteristics using descriptive statistics.

6.4.3 Safety/tolerability analysis

Since enrollment is concurrent with receiving the first study-product administration, all participants will have received at least 1 product administration and therefore will provide some safety data.

6.4.3.1 Solicited AEs

The number and percentage of participants experiencing each type of solicited AE sign or symptom (see Section 11.2.2) will be tabulated by severity and treatment arm and the percentages will be displayed graphically by arm. For a given sign or symptom, each participant's solicited AEs will be counted once under the maximum severity for all injection visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration or erythema, and systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between arms.

6.4.3.2 SAEs and unsolicited AEs

Unsolicited AEs (see Section 11.2.2) will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an unsolicited AE within a System Organ Class or within preferred-term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple unsolicited AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events, including severity, relationship to study product, time between onset and last study-product administration, and number of studyproduct administrations received.

6.4.3.3 Local laboratory values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see Section 9.8) will be tabulated by treatment arm for each post–study-product administration timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

6.4.3.4 Reasons for study-product administration discontinuation and early study termination

The number and percentage of participants who discontinue study-product administration and who terminate the study early will be tabulated by reason and treatment arm.

6.4.4 mAb concentration and PK analysis

6.4.4.1 Primary analyses of mAb concentrations

The primary analysis of serum concentration and PK of VRC01.23LS, PGDM1400LS, and PGT121.414.LS (primary objective 2) will be restricted to participants who received all scheduled administrations PP. Serum concentrations that fail the quality control of the assay, are from specimens collected outside of the visit window, or are from participants with HIV postacquisition may be excluded. The primary analysis of serum concentration will be descriptive and performed separately for each mAb. As an exploratory analysis, we will consider a pooled analysis across different dosing arms and investigate if the PK is modified by the dose. We will also compare the PK of VRC01.23LS administered alone with that of VRC01.23LS administered in combination with PGDM1400LS, and PGT121.414.LS.

A noncompartmental PK analysis will be performed on the concentration data. PK parameters may include, but are not limited to: AUC, Cmax, time to Cmax (Tmax), CL, Vd, terminal elimination rate constant (λz), and the terminal t1/2. Data will be summarized by each dose group and overall for CL, Vd, and t1/2. The potential for nonlinear PK will be determined by comparing the dose-adjusted ratios for Cmax and AUC within dosing groups. Graphical displays of the data (eg, boxplots, scatterplots, histograms, spaghetti plots) will be generated to visually explore distributional properties of the data. These summary statistics and graphical displays may be produced for each treatment arm and each timepoint separately. These summary statistics and PK parameters including half-life, will be compared to the published results of VRC01, VRC01LS, and VRC07-523LS.

6.4.5 Analysis of neutralization activity and correlation with serum concentrations

6.4.5.1 Primary analyses of neutralization magnitude-breadth (MB) curves

To address primary objective 3, at each specified timepoint, the area under the magnitude-breadth curve (AUC-MB) to a global panel of pseudoviruses (58) will be computed for each participant in the PP cohort with evaluable neutralization ID_{50} or ID_{80} data, as described in (59). Magnitude-breadth (MB) curves will be employed to display individual- and group-level response breadth as a function of magnitude. Response breadth is defined as the percentage of viruses in the panel with neutralization titer above certain thresholds. Comparisons of the MB curves among arms will be based on a nonparametric Wilcoxon rank sum test on the participant-specific AUC-MB and a Kolmogorov-Smirnov type test on the group-average MB curves. Simulations will be used to obtain two-sided p-values for the latter test. An alternative approach based on constructing a weighted-average score-like variable will be explored. Details of either approach will be described in the SAP.

6.4.5.2 Secondary analyses of correlations between serum concentrations and serum neutralization levels

To address secondary objective 1, pharmacodynamics (PD) models based on either linear or nonlinear mixed effects models will be performed to characterize the correlation between serum concentration (observed or population pharmacokinetic [popPK] model-predicted) and serum neutralization against each virus or the AUC-MB of serum neutralization against the panel. Data from all enrolled participants will be analyzed regardless of how many administrations and how much mAb dose they received (MITT analysis). Similar to the popPK analysis, data from specimens collected outside of the visit window may be included in the PK/PD analyses that account for the actual specimen collection time and the actual time and dose amount of each product administration. Since the exact date of HIV acquisition is unknown, any serum-level data from blood draws 4 weeks prior to a participant living with HIV's last seronegative sample and thereafter may be excluded. All data from participants living with HIV who have no seronegative samples postenrollment may be excluded from the analysis.

6.4.5.3 Secondary analyses of neutralization MB curves

To address secondary objective 2, at each specified timepoint, the AUC-MB to a panel of Env-pseudotyped reference viruses that are sensitive to all 3 bnAbs will be computed for all participants with evaluable neutralization ID50 or ID80 data, as described in (59). MB curves may be employed to display individual- and group-level response breadth as a function of magnitude.

6.4.6 Analysis of ADA and other non-neutralizing functional activities

For the analysis of ADAs (secondary objective 3), data from enrolled participants will be used regardless of how many administrations they received (MITT). For

exploratory objectives regarding mAb functionality, data from enrolled participants who received all scheduled administrations PP will be used. Assay results that are unreliable or from participants with HIV postacquisition will be excluded. Additional exploratory analyses examining the impact of confirmed positive ADA on PK will be described in the SAP.

6.4.7 General approach

Univariate and bivariate descriptive analyses of continuous assay data (eg, Luminex-based serum concentrations) will be performed using mean, median, SD, range, skewness, and Spearman's and Pearson's correlation coefficients, for example. Graphical displays of the data based on appropriate techniques (eg, boxplots, histograms, kernel density estimates, probability plots, two- or three-dimensional scatterplots, spaghetti plots) will be generated to visually explore distributional properties of the data as well as potential pairwise associations. Statistics and graphical displays will be produced for each treatment arm across timepoints.

Comparisons of continuous assay data between treatment groups or timepoints will be primarily performed using nonparametric rank-based tests, the Wilcoxon rank-sum test, or Friedman nonparametric two-way analysis of variance (ANOVA). In the event that the data appear normally distributed, the comparisons may be performed using appropriate parametric tests (eg, two-sample t-tests with unequal variances). Appropriate data transformations (eg, square-root, logarithmic) may be applied prior to testing hypotheses in order for key distributional assumptions (eg, normality, homoscedasticity [constancy of variance]) to be satisfied.

Analyses of categorical variables (eg, binary) will be conducted by constructing frequency tables. One such table will be produced for each treatment group and each timepoint. Crude response rates will be presented with their corresponding 95% CI estimates calculated using the score test method (60). Associations between categorical variables will be assessed using Barnard's (2 x 2 tables), Fisher's exact, or Chi-squared tests.

Analysis of longitudinal data may be performed using mixed effects models or generalized estimating equations (GEEs). These approaches allow describing outcome responses over several timepoints while accounting for potential intersubject heterogeneity. To achieve unbiased statistical estimation and inferences with nonparametric tests and generalized linear models fit by GEE methods, missing data need to be missing completely at random (MCAR). MCAR assumes that missingness does not depend on any observed or unobserved data (ie, the observed data is just a random sample of all the potential data). When missingness is negligible (eg, less than 20%), statistical methods (eg, nonparametric tests and GEE methods) based on the MCAR assumption can be used with limited impact on the analysis. When the frequency of missing data is more substantial, methods that require the MCAR assumption may give misleading results. In this situation, statistical analyses will be performed based

on appropriate modeling assumptions and will be adjusted using weighting methods, or combined with imputation, under the assumption that the missing data are missing at random (MAR). MAR assumes that the probability of an observation being missing only depends on the observed responses or covariates. Thus, this assumption is less stringent than the MCAR assumption. Weighting adjustments (eg, weighted GEE) and imputation methods are valid under MAR. We will consider including any of the available baseline predictors of the missing outcomes as covariates in statistical models. Please see Little and Rubin chapters 1, 3, and 6 (60) for elaborate definitions and examples of missing-data mechanisms and Ibrahim et al (61) for a review of missing-data methods in clinical studies.

Generalized linear models for response rates will use a binomial error distribution and for quantitative endpoints, a normal error distribution. We will assess repeated functional measurement using linear mixed-effects models. If functional activity outcomes are left- and/or right- censored, we will use Hughes' (62) linear mixed-effects models to accommodate censoring. In addition, exploratory analyses of repeated functional measurements may be done using weighted GEE (63) methods, which are valid under MAR. We will again consider including any of the available baseline predictors of the missing outcomes as covariates in statistical models.

6.4.8 Analyses prior to end of scheduled follow-up visits

Any analyses conducted prior to the end of the scheduled follow-up visits should not compromise the integrity of the trial in terms of participant retention or other study endpoint assessments.

6.4.8.1 Safety

During the course of the trial, unblinded analyses of safety data will be prepared approximately every 4 months for review by the SMB. Ad hoc safety reports may also be prepared for SMB review at the request of the HVTN 143/HPTN 109 PSRT.

7 Selection and withdrawal of participants

Participants will be adults who do not have HIV (seronegative), are in overall good health, comprehend the purpose of the study, and have provided written informed consent. Volunteers will be recruited and screened; those determined to be eligible, based on the inclusion and exclusion criteria, will be enrolled in the study. Final eligibility determination will depend on information available at the time of enrollment, including results of screening laboratory tests, medical history, physical examinations, and answers to self-administered and/or interview questions.

Occasionally, investigators encounter volunteers who may not be appropriate for enrollment even if they meet all inclusion/exclusion criteria. Unanticipated medical, psychiatric, occupational, or other conditions may make evaluation of safety and/or other endpoints difficult, making some volunteers poor candidates for retention. In these unusual instances, investigators should use good clinical judgment in considering a volunteer's overall fitness, taking care to avoid unconscious bias.

Determination of eligibility, taking into account all inclusion and exclusion criteria, must be made within 56 days prior to enrollment unless otherwise noted in Sections 7.1 and 7.2.

7.1 Inclusion criteria

General and demographic criteria

1. **Age** of 18 through 50 years
2. **Access to a participating CRS** and willingness to be followed for the planned duration of the study
3. Ability and willingness to provide **informed consent**
4. **Assessment of understanding (AoU):** volunteer demonstrates understanding of this study and completes a questionnaire prior to first study-product administration with verbal demonstration of understanding of all questionnaire items answered incorrectly
5. **Agrees not to enroll in another study** of an investigational research agent until completion of the last required protocol clinic visit.
6. **Good general health** as shown by medical history, physical exam, and screening laboratory tests

HIV-related criteria:

7. Willingness to receive **HIV test results**

8. Willingness to discuss **HIV acquisition** and amenable to HIV risk-reduction counseling.

9. Assessed by the clinic staff (using Appendix J) as having a low likelihood of HIV acquisition and is committed to avoid behaviors associated with a higher likelihood of acquiring HIV through the last required protocol clinic visit.

Laboratory inclusion values

Hemogram/complete blood count (CBC)

10. **Hemoglobin**

    - ≥ 11.0 g/dL for AFAB volunteers
    - ≥ 13.0 g/dL for AMAB volunteers and transgender men who have been on hormone therapy for more than 6 consecutive months
    - ≥ 12.0 g/dL for transgender women who have been on hormone therapy for more than 6 consecutive months
    - For transgender volunteers who have been on hormone therapy for less than 6 consecutive months, determine hemoglobin eligibility based on their sex assigned at birth

11. **White blood cell (WBC) count** = 2,500 to 12,000 cells/mm^3

12. **WBC differential** either within institutional normal range or with site clinician approval

13. **Platelets** = 125,000 to 550,000 cells/mm^3

Chemistry

14. **Chemistry panel**: **alanine aminotransferase** (ALT) < 1.25 times the institutional upper limit of normal (ULN) (ie, < 1.25 times the reference range upper limit) and **creatinine** < 1.1 times the institutional ULN (ie, < 1.1 times the reference range upper limit)

Virology

15. **Negative HIV-1 and -2 blood test**: Sites may use locally available assays that have been approved by HVTN and HPTN Laboratory Operations

16. **Negative Hepatitis B surface antigen (HBsAg)**

17. **Negative anti–Hepatitis C virus Abs (anti-HCV)** or negative HCV PCR if the anti-HCV is positive

Urine

18. **Negative or trace urine protein**

Reproductive status

19. **AFAB volunteers or volunteers who were intersex at birth and are capable of becoming pregnant (hereafter referred to as "persons of pregnancy potential"):** negative serum or urine beta human chorionic gonadotropin (β-HCG) pregnancy test(s) performed within 48 hours prior to initial study-product administration. Persons who are NOT of pregnancy potential due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing.

20. Persons of pregnancy potential must:

    - Agree to use effective contraception for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through the last required protocol visit. Effective contraception is defined as using one of the following methods:
        - Condoms (internal and external) with or without a spermicide,
        - Diaphragm or cervical cap with spermicide,
        - Intrauterine device (IUD),
        - Hormonal contraception,
        - Tubal ligation, or
        - Any other contraceptive method approved by the HVTN 143/HPTN 109 PSRT
        - Successful vasectomy in any AMAB partner (considered successful if a volunteer reports that an AMAB partner has [1] documentation of azoospermia by microscopy or [2] a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity postvasectomy); or,
    - Not be of pregnancy potential, such as having reached menopause (no menses for 1 year) or having undergone hysterectomy or bilateral oophorectomy; or,
    - Be sexually abstinent.

21. **AFAB volunteers or who were intersex at birth must also agree not to seek pregnancy through alternative methods**, such as oocyte retrieval, artificial insemination, or in vitro fertilization from at least 21 days prior to enrollment through 8 weeks until after the last required protocol clinic visit

7.2 Exclusion criteria

General

1. **Weight** < 35 kg or > 115 kg

2. **Blood products** received within 120 days before first study-product administration, unless eligibility for earlier enrollment is determined by the HVTN 143/HPTN 109 PSRT

3. **Investigational research agents** received within 30 days before first study-product administration

4. **Intent to participate in another study** of an investigational research agent or any other study that requires non-Network HIV Ab testing during the planned duration of the HVTN 143/HPTN 109 study

5. **Pregnant or breastfeeding**

Vaccines, Abs, and other injections or infusions

6. **HIV vaccine(s)** received in a prior HIV vaccine trial. Volunteers who have received control/placebo in an HIV vaccine trial are not excluded from HVTN 143/HPTN 109.

7. **SARS-CoV-2 vaccine(s)** received within 7 days prior to HVTN 143/HPTN 109 enrollment or planned within 7 days after enrollment.

8. **Jynneos vaccine for MPOX** received within 14 days prior to enrollment or planned within 14 days after enrollment.

9. **ACAM2000 vaccine for MPOX** received within 28 days prior to enrollment or, if ACAM2000 was received more than 28 days prior to enrollment, vaccination scab still present; or planned within 14 days after enrollment

10. **Receipt of humanized or human mAbs,** whether licensed or investigational.

11. **Previous receipt of mAbs targeting HIV (eg, cap256, VRC01, VRC01LS, VRC07-523LS, PGDM1400, PGDM1400LS, PGT121, PGT121.414.LS)**

Immune system

12. **Immunosuppressive medications** received within 30 days before first study-product administration (not exclusionary: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; [3] topical corticosteroids for mild, uncomplicated dermatological condition; or [4] a single course of oral/parenteral prednisone or equivalent at doses < 20 mg/day and length of therapy < 14 days, but completed at least 7 days prior to first infusion)

13. **Serious adverse reactions** to VRC01.23LS, PGDM1400LS, or PGT121.414.LS formulation components (see Section 8.2), including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain.

14. **Immunoglobulin** received within 60 days before first study-product administration (for mAb, see criterion 10 above)

15. **Autoimmune disease** (not exclusionary: volunteer with mild, stable, and uncomplicated autoimmune disease that does not require immunosuppressive medication and that, in the judgment of the CRS investigator, is likely not subject to exacerbation and likely not to complicate solicited and unsolicited AE assessments)

16. **Immunodeficiency**

Clinically significant medical conditions

17. **Clinically significant medical condition**, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health. A clinically significant condition or process includes but is not limited to:

    - Symptoms consistent with COVID-19 or known SARS-CoV-2 acquisition,
    - A process that would affect the immune response,
    - A process that would require medication that affects the immune response,
    - Any contraindication to repeated infusions or blood draws, including inability to establish venous access,
    - A condition that requires active medical intervention or monitoring to avert grave danger to the volunteer's health or well-being during the study period,
    - A condition or process (eg, chronic urticaria or recent injection or infusion with evidence of residual inflammation) for which signs or symptoms could be confused with reactions to the study product, or
    - Any condition specifically listed among the exclusion criteria.

18. **Any medical, psychiatric, or skin condition (eg, tattoos) or occupational responsibility** that, in the judgment of the investigator, would interfere with or serve as a contraindication to protocol adherence, assessment of safety or solicited AEs, or a participant's ability to give informed consent.

19. **Psychiatric condition that precludes compliance with the protocol.** Specifically excluded are persons with psychoses, ongoing risk for suicide, or history of suicide attempt within the past 3 years.

20. **Current anti-tuberculosis (TB) therapy**

21. **Asthma** other than mild, well-controlled asthma (symptoms of asthma severity as defined in the most recent National Asthma Education and Prevention Program [NAEPP] Expert Panel report).

    Exclude a volunteer who:

    - Uses a short-acting rescue inhaler (typically a beta 2 agonist) daily; or
    - Uses moderate/high-dose, inhaled corticosteroids; or
    - In the past year, has had either of the following:
        - Greater than 1 exacerbation of symptoms treated with oral/parenteral corticosteroids;
        - Emergency care, urgent care, hospitalization, or intubation for asthma.

22. **Diabetes mellitus** type 1 or type 2 (not exclusionary: type-2 cases controlled with diet alone or a history of isolated gestational diabetes)

23. **Hypertension**

    - If a person has been found to have elevated blood pressure or hypertension during screening or previously, exclude for blood pressure that is not well controlled. Well-controlled blood pressure is defined in this protocol as consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic, with or without medication, with only isolated, brief instances of higher readings, which must be ≤ 150 mm Hg systolic and ≤ 100 mm Hg diastolic. For these volunteers, blood pressure must be ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic at enrollment.
    - If a person has NOT been found to have elevated blood pressure or hypertension during screening or previously, exclude for systolic blood pressure ≥ 150 mm Hg at enrollment or diastolic blood pressure ≥ 100 mm Hg at enrollment.

24. **Bleeding disorder** diagnosed by a clinician (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions)

25. **Malignancy** (not exclusoinary: volunteer who has had malignancy excised surgically and who, in the investigator's estimation, has a reasonable assurance of sustained cure, or who is unlikely to experience recurrence of malignancy during the period of the study)

26. **Seizure disorder:** History of seizure(s) within past 3 years. Also exclude if volunteer has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.

27. **Asplenia:** any condition resulting in the absence of a functional spleen

28. History of **generalized urticaria**, **angioedema**, or **anaphylaxis** (not exclusionary: angioedema or anaphylaxis to a known trigger with at least 5 years since last reaction to demonstrate satisfactory avoidance of trigger)

7.3 Participant departure from study-product administration schedule or withdrawal (Part B)

This section concerns an individual participant's departure from the study-product administration schedule. Pause rules for the trial are described in Section 11.5.

7.3.1 Delaying study-product administrations for a participant (Part B)

Under certain circumstances, a participant's scheduled study-product administration will be delayed. Refer to the study-specific procedures (SSP) for further guidance regarding which procedures to conduct in these instances. The factors to be considered in such a decision include but are not limited to the following:

- Within 7 days prior to study-product administration
  - Receipt of systemic glucocorticoids (eg, prednisone or other glucocorticoids) or other immunomodulators (other than nonsteroidal anti-inflammatory drugs [NSAIDs])

- Within 7 days of study-product administration (ie, within 7 days prior to study-product administration or planned within 7 days after study-product administration)
  - Receipt of SARS CoV-2 vaccine

- Preinfusion abnormal vital signs or clinical symptoms that may mask assessment of study-product reaction.

- Intercurrent illness that is assessed by CRS PI (or designee) to require delaying study-product administration. The investigator may consult the HVTN 143/HPTN 109 PSRT.

- Pregnancy: study-product administration will be stopped while a participant is pregnant. If the participant is no longer pregnant (as defined by 2 consecutive negative tests) or breastfeeding and study-product administration can be performed within an appropriate visit window, study-product administration may resume with unanimous consent of the HVTN 143/HPTN 109 PSRT.

- Within 14 days of study-product administration (ie, within 14 days prior to study-product administration or planned within 14 days after study-product administration)
  - Receipt of Jynneos vaccine for Mpox
- Within 28 days prior to study-product administration or, if ACAM2000 was received more than 28 days prior to study-product administration, vaccination scab still present; or planned within 14 days after study-product administration
  - Receipt of ACAM2000 vaccine for MPOX

7.3.2 Participant departure from study-product administration schedule

Every effort should be made to follow the study-product administration schedule per the protocol. If a participant misses a study-product administration and the visit-window period for the study-product administration has passed, that study product cannot be given. The participant should be asked to continue study visits. (see Sections 7.3.1 and 7.3.3).

7.3.3 Discontinuing study-product administration for a participant

Under certain circumstances, an individual participant's study-product administrations will be permanently discontinued. Specific events that will result in stopping a participant's study-product administration schedule include:

- Coenrollment in a study with an investigational research agent (rare exceptions allowing for the continuation of study-product administrations may be granted with the unanimous consent of the HVTN 143/HPTN 109 PSRT)
- Clinically significant condition (ie, a condition that affects the immune system or for which continued study-product administrations and/or blood draws may pose additional risk), including but not limited to the following:
  - HIV acquisition
  - Any grade 4 local or systemic solicited or unsolicited AE that is subsequently considered to be related to study-product administration
  - Grade 3 clinical AE that is subsequently considered to be related to study-product administration with the exception of fever, vomiting, and subjective local and systemic symptoms. For grade 3 infusion-site erythema and/or induration, upon review, the HVTN 143/HPTN 109 PSRT may allow continuation of study-product administration
  - Any grade 3 or 4 lab abnormality confirmed by a repeated value that is subsequently considered to be related to study product;
  - SAE that is subsequently considered to be related to study-product administration

  - Clinically significant hypersensitivity or mAb reaction including, but not limited to, type 1 hypersensitivity reaction, urticaria, or serum sickness associated with study-product administration. Consultation with the HVTN 143/HPTN 109 PSRT is required prior to subsequent study-product administrations following any hypersensitivity reaction associated with study-product administration

- Investigator determination in consultation with Protocol Team leadership (eg, for repeated nonadherence to study staff instructions)

Participants discontinuing study product for reasons other than HIV acquisition should be counseled on the importance of continuing with the study and strongly encouraged to participate in follow-up visits and protocol-related procedures per the protocol for the remainder of the trial, unless medically contraindicated (see HVTN 143/HPTN 109 SSP).

Participants diagnosed with HIV during the study should be encouraged to participate in follow-up visits as indicated in Section 9.12.

7.3.4 Participant termination from the study

Under certain circumstances, an individual participant may be terminated from participation in this study. Specific events that will result in early termination include:

- Participant refuses further participation,

- Participant relocates and remote follow-up or transfer to another CRS is not possible,

- CRS determines that the participant is lost to follow-up,

- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff), or

- Any condition where termination from the study is required by applicable regulations.

8 Study product

Clinical Research Site (CRS) pharmacists should consult the Pharmacy Guidelines and Instructions for Division of AIDS (DAIDS) Clinical Trials Networks for standard pharmacy operations. The protocol schema is shown in Table 1-1. See the Investigator's Brochures (IBs) for further information about study products.

8.1 Study-product regimen

The schedule of study-product administration is shown in Section 1 and additional information is given below.

Part A

Group 1: VRC01.23LS 5 mg/kg to be administered via intravenous (IV) infusion at Month 0

Group 2: VRC01.23LS 20 mg/kg to be administered via IV infusion at Month 0

Group 3: VRC01.23LS 40 mg/kg to be administered via IV infusion at Month 0

Part B

Group 4: VRC01.23LS 5 mg/kg + PGT121.414.LS 5 mg/kg + PGDM1400LS 5 mg/kg to be administered via IV infusion sequentially in this order at Month 0 and Month 6

Group 5: VRC01.23LS 20 mg/kg + PGT121.414.LS 5 mg/kg + PGDM1400LS 5 mg/kg to be administered via IV infusion sequentially in this order at Month 0 and Month 6

Group 6: VRC01.23LS 20 mg/kg + PGT121.414.LS 20 mg/kg+ PGDM1400LS 20 mg/kg to be administered via IV infusion sequentially in this order at Month 0 and Month 6

Group 7: VRC01.23LS 40 mg/kg + PGT121.414.LS 5 mg/kg + PGDM1400LS 5 mg/kg to be administered via IV infusion sequentially in this order at Month 0 and Month 6

Group 8: VRC01.23LS 40 mg/kg + PGT121.414.LS 40 mg/kg + PGDM1400LS 40mg/kg to be administered via IV infusion sequentially in this order at Month 0 and Month 6

8.2 Study-product formulation

8.2.1 VRC01.23LS

VRC01.23LS will be supplied as 10-mL single-use glass vials with a 6.25 ± 0.1 mL fill volume at a concentration of 100 ± 10 mg/mL. Each vial contains a clear, colorless to yellow liquid, essentially free of visible particles (some opaque or translucent particles may be present). The formulation buffer is composed of 20 mM acetate phosphate, 25 mM sodium chloride, 150 mM arginine HCl, 5% sucrose, 0.2% polysorbate 80 at pH 5.8. Vials do not contain a preservative.

VRC07-523LS product label designates the long-term storage as -35ºC to -15ºC (-31ºF to 5ºF). The study product is described in further detail in the IB.

8.2.2 PGT121.414.LS

PGT121.414.LS will be supplied as 10-mL single-use glass vials with a 4.75-mL fill volume at a concentration of 100 mg/mL. Each vial contains a clear, colorless to yellow, preservative-free, sterile solution for injection. The formulation buffer is composed of acetate, sucrose, and polysorbate 80 at pH of 5.2. PGT121.414.LS product label designates the long-term storage as -35°C to -15°C (-31°F to 5°F).

8.2.3 PGDM1400LS

PGDM1400LS will be supplied as 10-mL single-use glass vials with a 4.75 ± 0.1 mL fill volume at a concentration of 100 mg/mL. Upon thaw, each vial contains a clear, colorless to yellow solution for injection, which is essentially free from foreign particles, but some opaque or translucent particles may be present. The formulation buffer is composed of 10 mM acetate, 9% w/v sucrose, 0.01% weight per volume (w/v) polysorbate 80 at pH 5.2. It does not contain a preservative.

The product is stored frozen at -35°C to -15°C in a qualified, continuously monitored, temperature-controlled freezer until use. The study product is described in further detail in the IB.

8.3 Preparation of study products

Prior to preparation of the first infusion (enrollment visit), a new prescription will be sent to the pharmacy. The prescription MUST contain the participant's weight based on the participant's weight at the most recent visit where weight was measured (this includes screening). If this information is NOT on the prescription, the prescription will be returned to the clinic from the pharmacy to be completed appropriately prior to the pharmacist beginning preparation of study product. Subsequent visit weights (based upon the participant's weight at the most recent visit where weight was measured) must be communicated to the pharmacy in writing prior to the day of the visit. Any changes in weight of more than 10% (between the prior weight and the weight on the day of the infusion visit) will

require an updated visit weight communication to the pharmacy in writing so that product can be prepared based on that weight change.

Pharmacists must follow appropriate aseptic technique and sterile preparation procedures as outlined in United States Pharmacopeia (USP) <797> Pharmaceutical Compounding – Sterile Preparations, utilizing a pharmacy biosafety cabinet/isolator or better. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, masks, and safety glasses, must be followed. Pharmacists should follow the requirements of their country, institution, and pharmacy regulatory authority regarding these procedures.

Any unused portion of study product will not be used for another participant. Any empty vials, unused portion of entered vials, or unused solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

8.3.1 VRC01.23LS

VRC01.23LS is a highly concentrated protein solution and may develop white, opaque-to-translucent particles after thawing.

8.3.1.1 Thawing instructions

1. Thaw vial(s) for a minimum of 1 hour at controlled room temperature (maximum 27°C) after removing from the freezer.

2. Keep the material at room temperature during the entire preparation period until use, up to the maximum storage times described in #4 below.

3. Prior to preparation for administration, swirl vials for 30 seconds to resuspend any visible particles, avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, return the vials to 2°C to 8°C storage. If the particles redissolve within the maximum storage times described in #4 below, vials may be used for product preparation. If particles continue to be observed, do not use the vials.

4. Thawed vials may be stored for cumulatively up to 24 hours at controlled room temperature (maximum 27°C) and up to 2 weeks (14 days) at 2°C to 8°C. Product may not be stored in direct sunlight. If stored at 2ºC to 8ºC, vials must be equilibrated at controlled room temperature (maximum 27ºC) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation. Vials should not be refrozen after thawing.

8.3.1.2 VRC01.23LS weight-based dose IV infusion preparation

1. Calculate the total dose (mg) of VRC01.23LS required based on participant's weight (in kg). Remove the minimum number of thawed, particle-free VRC01.23LS vials from storage, as well as an appropriately sized IV

container (bag/glass bottle) containing 100 mL of 0.9% sodium chloride for injection, USP, that will also permit the addition of the required calculated volume of VRC01.23LS.

2. Gently swirl thawed vials for 30 seconds, avoiding foaming. DO NOT SHAKE VIALS. Keep the vials upright at all times until ready to withdraw the contents. Do not invert the vials during inspection.

3. Observe vials for particles. If particles are observed, refer to the thawing instructions described above in Section 8.3.1.1

4. Using aseptic technique, add the calculated volume of VRC01.23 LS to the IV container with 100 mL of sodium chloride for injection, 0.9 USP. Record this as the study-product preparation time.

5. The prepared VRC01.23LS IV container may be stored at 2°C to 8°C or at ambient temperature (maximum 27°C) for up to 4 hours total, including the infusion time. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, prepared product must be equilibrated at controlled room temperature (maximum 27°C) for a minimum of 30 minutes prior to product administration.

8.3.2 PGT121.414.LS

8.3.2.1 Thawing instructions

1. Thaw vial(s) at room temperature and hold for at least 30 minutes post-thaw (no ice crystals present). Vials must not be moved directly from the freezer to storage at 2°C to 8°C.

2. Keep the material at room temperature during the entire preparation period until use, up to the maximum storage times described in #4 below.

3. Prior to preparation for administration, swirl vials for 30 seconds to resuspend any visible particles, avoiding foaming. DO NOT SHAKE THE VIALS. If some white to translucent particles continue to be observed, vials may be used for the preparation of the IV or subcutaneous (SC) product.

4. Thawed vials may be stored for up to 24 hours at room temperature (maximum 27°C). If vials are not used within that time, they may be refrigerated for up to 2 weeks (14 days) at 2°C to 8°C and should be used within 8 hours of any subsequent return to room temperature (maximum 27°C). Refrigerated product must be equilibrated at room temperature (maximum 27°C) for a minimum of 30 minutes prior to use.

8.3.2.2 PGT121.414.LS weight-based dose IV infusion preparation

1. Calculate the total dose (mg) of PGT121.414.LS required based on the participant's weight (in kg). Remove the minimum number of thawed

PGT121.414.LS vials from storage, as well as an appropriately sized IV container (bag/glass bottle) containing 100 mL of 0.9% sodium chloride for injection, USP, that will also permit the addition of the required calculated volume of PGT121.414.LS.

2. Gently swirl thawed vials for 30 seconds, avoiding foaming. DO NOT SHAKE VIALS. Keep the vials upright until ready to withdraw the contents. Do not invert the vials during inspection.

3. Using aseptic technique, remove the air from the IV container and then add the calculated volume of PGT121.414.LS to the IV container with 100 mL of sodium chloride for injection, 0.9 % USP. Record this as the study-product preparation time.

4. The prepared PGT121.414.LS product may be stored at 2°C to 8°C for up to 24 hours or at room temperature (maximum 27°C) for a maximum of 4 hours, including the administration time. If stored at 2°C to 8°C, prepared product must be equilibrated at room temperature (maximum 27°C) for a minimum of 30 minutes prior to product administration.

8.3.2.3 Labeling of study product

Label the study product as follows:

- Participant identifier(s)
- Participant weight (in kg) for weight-based dosing
- Study-product name
- Total dose (mg)
- Final volume (mL)
- Route (IV)
- Beyond-use date and time
- Any additional information required by jurisdiction

1.1.1 PGDM1400LS

8.3.2.4 Thawing instructions

1. Remove PGDM1400LS vials from the freezer and thaw at controlled room temperature (maximum 27°C).

2. After thawing, the PGDM1400LS vials may be stored at 5°C ± 3°C for up to 14 days and at 25°C ± 2°C for up to 24 hours. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, vials must be equilibrated at controlled room temperature (15°C to 27°C) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation. PGDM1400LS vials should not be refrozen after thaw.

8.3.2.5 PGDM1400LS weight-based dose IV infusion preparation

1. Calculate the total dose (mg) of PGDM1400LS required based on the participant's weight (in kg). Obtain the minimum number of thawed PGDM1400LS vials, as well as an appropriately sized IV container (bag/glass bottle) containing 100 mL of 0.9% sodium chloride for injection, USP, that will also permit the addition of the required calculated volume of PGDM1400LS.

2. Using an 18G needle, withdraw the calculated volume of PGDM1400LS into a sterile syringe.

3. Using aseptic technique, remove the air from the IV container and then add the withdrawn volume of PGDM1400LS to the IV container with 100 mL of 0.9% sodium chloride for injection, USP. Record this as the study-product preparation time.

4. Gently mix the prepared IV container. Ensure there are no visible particulates in the IV container.

5. After product preparation in IV bags, the prepared PGDM1400LS product may be stored at 2°C to 8°C for up to 24 hours or at controlled room temperature (15°C to 27°C) for a maximum of 4 hours total, including the infusion time. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, prepared product must be equilibrated at controlled room temperature (15°C to 27°C) for a minimum of 30 minutes prior to product administration.

8.4 Administration

The container prepared by the pharmacy will include the weight that was used for preparation of the study product. The clinician responsible for administration will check the container label and confirm that the participant identifier(s) are correct and that the weight listed on the container label is within 10% of the participant's current actual weight.

In Groups 4-8, 3 separate IV containers each containing 1 study product will be administered sequentially.

8.4.1 General considerations for IV infusion study-product administration

For all IV infusions:

- A 1.2 micron in-line filter must be used for IV product administration. Filters must comply with the specifications described in the HVTN 143/HPTN 109 study-specific procedures (SSP).
- Once the in-line filter is added to the tubing, prime the administration set with 0.9% sodium chloride for injection, USP.
- Refer to the HVTN 143/HPTN 109 SSP for further information on IV administration.

8.4.2 VRC01.23LS (IV infusion)

VRC01.23LS will be administered IV over approximately 30 to 60 minutes.

8.4.3 PGT121.414.LS (IV infusion)

PGT121.414.LS will be administered IV over approximately 30 to 60 minutes.

8.4.4 PGDM1400LS (IV infusion)

PGDM1400LS will be administered IV over approximately 30 to 60 minutes.

8.5 Acquisition of study products

VRC01.23LS is provided by the Dale and Betty Bumpers Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Department of Health and Human Services (DHHS) (Bethesda, MD, USA).

PGT121.414.LS is provided by DAIDS, NIAID, NIH, DHHS (Bethesda, MD, USA)

PGDM1400LS is provided by DAIDS, NIAID, NIH, DHHS (Bethesda, MD, USA).

Once a CRS is protocol registered, the pharmacist can obtain study products from the NIAID Clinical Research Products Management Center (CRPMC) by following the ordering procedures outlined in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

Filter needles, in-line filters, infusion sets, infusion pumps, tubing, and 0.9% sodium chloride for injection, USP will be locally sourced by the site. Refer to the

study-product considerations section of the HVTN 143/HPTN 109 SSP for product-specific reference numbers.

8.6 Pharmacy records

The CRS pharmacist is required to maintain complete records of all study products. The pharmacist of record is responsible for maintaining randomization codes and randomization confirmation notices for each participant in a secure manner.

8.7 Final disposition of study products

All unused study products must be destroyed after the study is completed or terminated unless otherwise instructed by the study sponsor. The procedures are included in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

9 Clinical procedures

The schedule of clinical procedures is shown in Appendix H and Appendix I.

Procedures are in place so that study visits may be conducted remotely, such as via phone, text message, email, or other electronic means, in lieu of, or in combination with, in-person visits at the CRS. Furthermore, some visit procedures may be conducted outside the CRS (eg, PK sampling; see HVTN 143 /HPTN 109 SSP for additional details). Direct data entry or direct data capture of study data into the study database is allowed when capturing information from the participant. Study data may also be sourced from electronic or paper source documents prior to being entered into the study database (see HVTN 143/HPTN 109 SSP).

9.1 Informed consent

Informed consent is the process of working with participants so that they fully understand what will and may happen to them while participating in a research study. The informed consent form (ICF) documents that a participant: (1) has been informed about the potential risks, benefits, and alternatives to participation and (2) is willing to participate in the study. Informed consent encompasses all written or verbal study information CRS staff provide to the participant, before and during the trial. CRS staff will obtain informed consent of participants according to HVTN and HPTN policies and procedures, as well as per the CRS's SOP on the informed consent process.

The informed consent process continues throughout the study. Key study concepts should be reviewed periodically with the participant, and the review should be documented. At each study visit, CRS staff should consider reviewing the procedures and requirements for that visit and for the remaining visits. Additionally, if any new information is learned that might affect the participants' decisions to stay in the trial, this information will be shared with trial participants. If necessary, participants will be asked to sign revised ICFs as directed by the IRB/EC.

A CRS may employ recruitment efforts prior to the participant consenting. For example, some CRSs use a telephone script to prescreen people before they come to the clinic for a full screening visit. Participants must sign a screening or protocol-specific consent before any procedures are performed to determine eligibility. CRSs must submit recruitment and prescreening materials to their IRB/EC and any applicable RE for human participants protection review and approval.

Note: As defined in the DAIDS Protocol Registration Manual, an RE is "any entity/body that has the power to regulate which includes authorities that review submitted clinical data and those that conduct inspections. These are sometimes referred to as competent authorities. These are entities/bodies whose

approval/authorization/acknowledgment of a clinical trial is required for conducting a clinical trial. Any organization whose approval is required prior to a CRS's participation in DAIDS funded and/or Sponsored Clinical Trial. Includes but not limited to approvals from state/national health systems and administrative bodies, drug agencies etc. (DAIDS adopted from ICH E6)." CRSs are responsible for complying with the requirements of their applicable REs.

9.1.1 Screening consent form

Without a general screening consent, screening for a specific study cannot take place until the CRS receives protocol registration from the DAIDS RSC Protocol Registration Office.

Some CRSs have approval from their IRB/EC and any applicable RE to use a general screening consent form that allows screening for an unspecified HIV prevention clinical trial. In this way, CRS staff can continually screen potential participants and, when needed, proceed quickly to obtain protocol-specific enrollment consent. Sites conducting general screening or prescreening approved by their IRB/EC and any applicable RE may use the results from this screening to determine eligibility for this protocol, provided the tests are conducted within the time periods specified in the eligibility criteria.

9.1.2 Protocol-specific consent forms

The protocol-specific consent forms describe the study products to be used and all aspects of protocol participation, including screening and enrollment procedures. Sample protocol-specific consent forms for the main study are located in Appendix A and Appendix B. A separate sample consent form for other uses of specimens is located in Appendix D.

Each CRS is responsible for developing a protocol-specific consent form(s) for local use, based on the sample protocol-specific consent forms in Appendix A, Appendix B, and Appendix D. The consent form(s) must be developed in accordance with requirements of the following:

- CRS's IRB/EC and any applicable REs,
- CRS's institution, and
- Elements of informed consent as described in Title 45, CFR Part 46, Title 21 CFR, Part 50, and ICH E6(R2) Good Clinical Practice: Consolidated Guidance 4.8.

Study sites are strongly encouraged to have their local CABs review their sites-specific consent forms. This review should include, but should not be limited to, issues of cultural competence, local language considerations, and the degree to which the sample informed consent form (SIC0)F is understandable to a layperson.

The SICFs include instructions for developing specific content.

Regarding protocol registration, sites should follow procedures outlined in the current version of the DAIDS Protocol Registration Manual.

9.1.3 Assessment of Understanding (AoU)

Study staff is responsible for ensuring that participants fully understand the study before enrolling them. This process involves reviewing the ICF with the participant, allowing time for the participant to reflect on the procedures and issues presented, and answering all questions completely.

An AoU is used to document the participant's understanding of key concepts in this clinical trial. The participant must complete the AoU before enrollment. Staff may provide assistance in reading and understanding the questions and responses, if necessary. Participants must verbalize understanding of all questions answered incorrectly. This process and the participant's understanding of the key concepts should be recorded in source documentation at the site.

IRB/EC and any applicable RE may require that a participant has signed either a screening or protocol-specific consent document prior to administering the AoU. The consent process (including the use of the AoU) should be explained thoroughly to the IRB/EC and any applicable RE, whose recommendations should be followed.

9.2 Pre-enrollment procedures

Screening may occur over the course of several contacts/visits, up to and including before study-product administration on day 1. All inclusion and exclusion criteria must be assessed within 56 days before enrollment, unless otherwise specified in the eligibility criteria (or below in this section).

After the appropriate informed consent has been obtained and before enrollment, the following procedures are performed:

- Medical history, documented in the case history record;
- Assessment of whether the volunteer has a low likelihood of acquiring HIV (see Appendix J);
- Complete physical examination, including height, weight, and vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Assessment of concomitant medications the volunteer is taking, including prescription and nonprescription drugs, vitamins, topical products,

alternative/complementary medicines (eg, herbal and health food supplements), recreational drugs, vaccinations, and allergy shots;

- Laboratory tests, including:
  - Screening HIV,
  - HBsAg,
  - Anti-HCV Abs,
  - Syphilis,
  - CBC with differential,
  - Chemistry panel (ALT, creatinine),
  - Urine dipstick (urinalyses, if indicated; see Section 9.7), and
  - Urine or serum pregnancy test (volunteers who are of pregnancy potential); persons who are not of pregnancy potential due to having undergone total hysterectomy with bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing;
- Administration of behavioral assessment questionnaire;
- Obtaining volunteer demographics in compliance with the NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research, Aug. 8, 2001 (available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html);
- Counseling on HIV testing and risk reduction, performed in compliance with the US Centers for Disease Control and Prevention (CDC)'s current guidelines or other local guidelines for HIV counseling, testing, and referral as described in Section 9.5; and
- Discussion of reproductive status and pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and reproductive status are described in study inclusion criteria. Discussion of contraception includes advising a participant who is of pregnancy potential and who reports no current sexual activity that could lead to that participant becoming pregnant to have a plan to begin adequate birth control. This plan would be put to use if, during the study, the participant becomes sexually active in a way that could lead to that participant becoming pregnant.

9.2.1 Use of screening results from another HVTN or HPTN study

If a participant screens for an HVTN or HPTN study at the same CRS but then does not join that study, screening results from that effort may be applied to the screening for this protocol, as long as the screening was done under participant consent, the participant has signed a consent form to begin screening for this

study, and the tests were conducted within the time periods specified in the eligibility criteria (see Sections 7.1 and 7.2).

9.3 Enrollment and study-product administration visits

Once a volunteer has consented to trial participation and is found to meet all eligibility criteria (see Sections 7.1 and 7.2), the CRS requests the randomization assignment via a Web-based randomization system. Enrollment is simultaneous with first study-product administration. In general, the time interval between randomization and enrollment should not exceed 4 working days. However, circumstances may require a participant's enrollment visit to be changed. This may exceed the 4-day randomization time limit with approval from the clinical trial manager/clinical research manager.

At **all study-product administration visits**, the following procedures are performed **before study-product administration:**

- Abbreviated physical examination, including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints;
- Assessment of baseline solicited AEs;
- Assessment of concomitant medications (as described in Section 9.2);
- Assessment of any new or unresolved unsolicited AEs/intercurrent illnesses; and
- Clinical laboratory tests including:
  - CBC with differential;
  - Chemistry panel (ALT, aspartate aminotransferase [AST], alkaline phosphatase [Alk Phos], and creatinine); and
  - Urine or serum pregnancy test (for participants who are of pregnancy potential). Persons who are NOT of pregnancy potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. For pregnant participants, see Section 9.11.

Following completion of all procedures in the preceding list, and if available results indicate that study-product administration may proceed, study product is administered (see Sections 8.3 and 8.4).

Administration of all infusions during a study-product administration visit must be accomplished within 1 calendar day.

Immediately following study-product administration, the participant remains in the clinic for observation for about 1 hour. See the HVTN 143/HPTN 109 SSP for details regarding study-product administration visit procedures. Before leaving the clinic, the participant is given the Participant Diary and is instructed on how to complete it. The CRS will make arrangements to be in contact with the participant as described in Section 9.8.

The following procedures will be performed at **all study-product administration visits**. These procedures may be performed **prior to or following study-product administration**:

- Risk-reduction counseling (as described in Section 9.5);
- For participants of pregnancy potential, contraception status assessment (as described in Sections 9.2 and 9.6). For persons who are confirmed pregnant, contraception status assessment is not required; and
- Assessment of new or unresolved social impacts (CRS staff will ask participant about the status of any unresolved social impacts and if they have experienced any new social impacts as a result of the trial participation).

The following procedures will be performed at all infusion visits following study-product administration:

- Acceptability questionnaire (see Appendix H and Appendix I); and
- Drug concentrations/detection collection (see Appendix F and Appendix G).

Additional procedures will be performed at scheduled visits as specified in Appendix H and Appendix I:

- HIV assessment, including pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate; and
- Specimen collection (should be completed per Appendix F and Appendix G).

9.3.1 Managing Ab reactions

Since VRC01.23LS, PGT121.414.LS and PGDM1400LS are human mAbs, rather than murine or chimeric mAbs, which target a viral antigen, and rather than human-cell surface antigens, serious Ab reactions are expected to be rare. Nevertheless, participants will be closely monitored in the clinic during study-product administration and during a post–study-product-administration observation period.

CRS staff are trained to recognize suspected Ab reactions and provide immediate medical care consistent with the HVTN 143/HPTN 109 SSP. Medications used to treat Ab reactions may include acetaminophen, antihistamines, and/or corticosteroids. CRSs are also equipped with additional emergency medical supplies to provide other immediate medical intervention, if indicated, and are near medical emergency services. Should the need arise, CRSs may transfer the participant, once stabilized, to a tertiary care center for further management.

The following procedures should be performed after an Ab reaction:

- Ab reaction clinical assessment; and
- Ab reaction blood collection.

For detailed management of Ab reactions, see the HVTN 143/HPTN 109 SSP.

9.4 Follow-up visits

The following procedures are performed at **scheduled follow-up visits,** as specified in Appendix H and Appendix I:

- Risk-reduction counseling (as described in Section 9.5);
- For participants of pregnancy potential, contraception status assessment (as described in Sections 9.2 and 9.6). In persons who are confirmed pregnant, contraception status assessment is not required;
- Assessment of new or unresolved social impacts (CRS staff will ask participant about the status of any unresolved social impacts and if they have experienced any new social impacts as a result of the trial participation);
- Assessment of new or continuing concomitant medications (as described in Section 9.2);
- Assessment of new or unresolved AEs/intercurrent illnesses;
- Administration of the social impact assessment questionnaire (types of impacts assessed involve personal relationships, health insurance, life insurance, educational or employment opportunities, housing, immigration, or travel);
- Administration of a questionnaire that asks the participant about any HIV testing they may have received outside of the study;
- HIV assessment, including pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;

- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Abbreviated physical examination, including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints;
- Complete physical examination, including weight and vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Specimen collection (should be completed per Appendix F and Appendix G); and
- Clinical laboratory tests including:
  - CBC with differential;
  - Chemistry panel (ALT, AST, Alk Phos, and creatinine);
  - Urine dipstick (urinalysis if appropriate; see Section 9.7); and
  - Urine or serum pregnancy test (for participants who are of pregnancy potential). Persons who are NOT of pregnancy potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. During follow-up in persons who are confirmed pregnant, contraception status assessment is not required, unless clinically indicated.

9.4.1 Interim contacts

CRSs may report safety information obtained at a contact other than the regularly scheduled visits. These contacts are reported as interim visits.

9.5 HIV counseling and testing

HIV counseling will be performed in compliance with the CDC's guidelines or other local guidelines for HIV counseling and referral. HIV testing will be performed in accordance with the protocol-specific HIV testing algorithm following enrollment.

Participants will be counseled routinely during the trial on the avoidance of HIV acquisition.

Potential participants identified during screening as having acquired HIV are not enrolled. Potential and enrolled participants identified as having HIV will be referred for medical treatment, counseling, and management of their HIV. With respect to enrolled participants who acquire HIV during the study, see Section 9.12.

It is theoretically possible that an anti-HIV mAb may suppress viral replication, which can reduce the ability to detect HIV, even if a person has actually acquired HIV.

An anti-HIV mAb is not likely to directly affect the assays used to detect HIV-1 acquisition.

9.6 Monoclonal Ab-associated reactivity

Tests of human plasma containing anti-HIV mAbs have been conducted using a variety of commercially available HIV test kits. At high plasma concentrations, reactive or indeterminate results have been observed on some test kits. See the HVTN 143/HPTN 109 SSP for further detail. Thus, there is a possibility that receipt of the study product will cause a reactive result on some currently available HIV test kits, especially if testing occurs close to study-product administration timepoints.

Study staff will advise study participants to confine their HIV testing while in the study to that provided through the CRS. Staff will also inform study participants of the likelihood of routine HIV testing being offered or performed outside the study CRS at emergency rooms, clinics, and medical offices, and will inform participants of their right to opt out of HIV testing outside the study site. CRS staff should inform study participants if local and/or state/regional policies and regulations permit medical providers to perform HIV testing without first informing patients. If this is the case, then CRS staff should advise study participants that they may decline testing preemptively. CRS staff should also inform participants if positive results must be reported to local public health authorities. CRS staff should provide participants with CRS contact information and should encourage participants to ask medical providers to contact the CRS. The CRS can verify that the participant is in an HIV mAb clinical trial and should only be tested at the study CRS.

9.7 Contraception status

Contraception status is assessed and documented at clinic visits indicated in Appendix H and Appendix I for a participant who is of pregnancy potential. Prior to enrollment and throughout the study, staff will ask participants to verbally confirm their use of adequate contraceptive methods. A participant who is of pregnancy potential should be reminded at all scheduled clinic visits of the importance of using contraception and should be referred to specific counseling, information, and advice as needed (specific contraception requirements are listed in Section 7.1). This reminder should be documented in the participant's study record.

Self-reported infertility,including having reached menopause (no menses for 1 year) or having undergone hysterectomy or bilateral oophorectomy, must be documented in the participant's study record.

9.8 Urine testing

Dipstick testing must include the following required elements: glucose, protein, and hemoglobin. The examination is performed on urine obtained by clean catch.

If the screening dipstick is transiently abnormal due to nonurinary bleeding (eg, menstruation) or infection, document this issue in the participant's source documentation. For infection, provide appropriate treatment and/or referral and document this in the participant's chart. Following resolution, repeat the dipstick and, if within the eligibility limits specified in the protocol, the participant may be enrolled.

Follow-up visit dipstick testing should be deferred if a participant is experiencing nonurinary bleeding (eg, menstruation) but should be performed as soon as possible. If a follow-up visit dipstick is abnormal due to a participant's nonurinary bleeding (eg, menstruation) document in the comment section of the case report form (CRF) and repeat the dipstick once the participant is no longer experiencing nonurinary bleeding. A micro-urinalysis is not required. If a follow-up visit dipstick or micro-urinalysis is abnormal due to infection, provide appropriate treatment and/or referral and document this in the participant's source documentation. See the Urinalysis Sample Collection, Interpretation, Management, and Reporting section of the Ab Manual of Operations (MOP) for further details.

9.9 Assessments of solicited AEs

For all participants, baseline assessments are performed before, and solicited AE assessments are performed after each study-product administration. All solicited AEs are graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, except as noted in Section 11.2.2. See HVTN 143/HPTN 109 SSP for further details.

The solicited AE assessment period is 3 full days following each study-product administration, per the assessment schedule shown in Table 9-1. Participants are instructed to record symptoms using a Participant Diary. The CRS staff and the participant will be in contact after the solicited AE assessment period, or sooner if indicated. In general, a participant who self-reports any post–study-product administration reactions greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved. Clinic staff will follow and collect resolution information for any solicited AE sign or symptoms that has not resolved within the solicited AE assessment period.

Solicited AEs are reported using CRFs that correspond to the time of assessment in Table 9-1. Solicited AE assessments include assessments of systemic and local symptoms, and study-product–related lesions. Events not listed on a CRF, with an onset after the solicited AE assessment period (day of study-product administration and 3 full days after), or meeting SAE/unsolicited AEs requiring expedited reporting according to DAIDS criteria, are recorded on an unsolicited AE log CRF.

Table 9-1 Schedule of solicited AE assessments

Day	Time	Performed by
1[a]	Baseline: Before study-product administration	CRS clinician
	Early: 25-60 minutes after study-product administration (the last/third study infusion in Part B)	CRS clinician
	Between early assessment and 11:59 pm day 1	CRS clinician or participant
2-4[b]	Between 12:00 am and 11:59 pm on the respective day	CRS clinician or participant

[a] Day of study-product administration
[b] New or unresolved solicited AEs present on day 4 are followed until resolution

9.9.1 Assessment of systemic and local symptoms

Systemic symptoms to be assessed as solicited AEs in this trial include increased body temperature, malaise and/or fatigue, myalgia, headache, chills, arthralgia, nausea, urticaria, nonexertional dyspnea, nonexertional tachycardia (assessed by CRS staff, not by the participant), generalized pruritus, facial flushing, and unexplained diaphoresis. Local symptoms include pain and/or tenderness at the infusion site. The daily maximum severity reached for each symptom during the assessment period is reported.

Body temperature is measured by oral or infrared thermometry. All temperatures must be measured by nonaxillary thermometry. This includes temperatures taken in the clinic, as well as temperatures taken by participants during the solicited AE period.

Temperature is reported in degrees Celsius. A measurement is taken once daily during the assessment period and should be repeated if participant is feeling feverish.

9.9.2 Assessment of IV infusion site

Typical infusion-site reactions are erythema/redness and induration/swelling. The maximum diameter measurement for all infusion-site reactions is recorded.

All infusion-site reactions are monitored until resolution. Reactions with areas with diameters ≥ 5 cm are followed daily; otherwise, the frequency of follow-up is based on clinician judgment. See the HVTN 143/HPTN 109 SSP for details.

9.10 Visit windows and missed visits

Visit windows are shown in Appendix K. The procedures for documenting missed visits and out-of-window visits are described in the HVTN 143/HPTN 109 SSP.

If a participant misses a scheduled visit, the CRS staff should either attempt to bring the participant in to the CRS or conduct the visit remotely as soon as possible to complete the required safety assessments and other procedures. See the SSP for more details.

If a missed visit required study-product administration or if study-product administration must be permanently discontinued, please refer to Section 7.3.2 and Section 7.3.3 for resolution.

9.11 Early termination visit

In the event of early participant termination, CRS staff should attempt to complete the following assessments, as appropriate: a final physical examination, clinical laboratory tests (including urine dipstick, CBC with differential, and chemistry panel) (see Section 7.1), pregnancy testing (for persons who are confirmed pregnant, pregnancy testing is not required unless clinically indicated), social impact assessment, and HIV test. For participants who have a confirmed diagnosis of HIV, see Section 9.12.

9.12 Pregnancy

If a participant becomes pregnant during the course of the study, no more infusions of study product will be given, but remaining visits and study procedures should be completed unless medically contraindicated or applicable regulations require termination from the study. During follow-up in persons who are confirmed pregnant, pregnancy testing is not required unless clinically indicated. If the participant terminates from the study prior to the pregnancy outcome, the CRS should make every effort to keep in touch with the participant in order to ascertain the pregnancy outcome. Pregnancies and pregnancy outcomes will be reported. If the participant is no longer pregnant, refer to Section 7.3.1.

See Pregnancy Management and Reporting section of the Ab MOP for further details.

9.13 HIV acquisition during the study

If a participant acquires HIV during the course of the study, no additional study product will be administered. Participants will be encouraged to continue scheduled study visits for up to 24 weeks following their last study-product

administration. Follow-up duration for participants diagnosed with HIV may be adjusted in consultation with the CRS investigator and the HVTN 143/HPTN 109 PSRT (eg, to avoid interference with participant initiation of HIV treatment). At post-acquisition follow-up visits, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests will be collected (for persons who are confirmed pregnant, pregnancy testing is not required unless clinically indicated). In addition, some clinic procedures may be modified or discontinued (see Appendix F and Appendix G). These individuals may also be referred to appropriate ongoing clinical trials or observational studies.

See the HIV Infection section in the Ab MOP for further details.

10 Laboratory

10.1 CRS laboratory procedures

The HVTN 143/HPTN 109 Site Lab Instructions and SSP provide further guidelines for operational issues concerning the clinical and processing laboratories. These documents include guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

Tube types for blood collection are specified in Appendix F and Appendix G. For tests performed locally, the local lab may assign appropriate tube types.

In specific situations, the blood-collection tubes may be redirected to another laboratory or may require study-specific processing techniques. In these cases, special laboratory instructions will be posted on the protocol-specific section of the HVTN website.

Of note, all assays described below are performed as research assays and are not approved for use in medical care. Results from these assays are not made available to participants or medical professionals to guide treatment decisions.

10.2 Total blood volume

Required blood volumes per visit are shown in Appendix F and Appendix G. Not shown is any additional blood volume that would be required if a safety lab needs to be repeated, or if a serum pregnancy test needs to be performed. The additional blood volume would likely be minimal. The total blood volume drawn for each participant will not exceed 500 mL in any 56-day (8-week) period.

10.3 VRC01.23LS, PGT121.414.LS, and PGDM1400LS concentrations

VRC01.23LS, PGT121.414.LS, and PGDM1400LS concentrations will be measured in a serum collected at prespecified timepoints. A quantitative immunoassay will be used to determine the concentration of each mAb. Ultra-sensitive bead-based analyses enable a broad dynamic range and higher sensitivity (eg, for the anti-idiotype mAb, 5C9, the lower limit of quantification is approximately 50 pg/mL). The operational sensitivity of the quantitative assays will be determined for the clinical-grade VRC01.23LS, PGT121.414.LS, and PGDM1400LS used for this study. For multiplexed PK measurements, interference testing will be included as part of the qualification/validation. The mAb concentrations may be normalized relative to total protein.

10.4 Neutralizing antibody (nAb) assay

HIV-1–specific nAb assays will be performed on serum samples from study participants taken at postadministration timepoint(s) and at baseline. The TZM-bl assay will test neutralization of mAb-specific viruses (1 virus per mAb). The assay will also test the neutralization of a panel of viruses that exhibit a range of known sensitivities to VRC01.23LS, PGT121.414.LS, and PGDM1400LS. The viruses will be selected from a global and/or clade-specific panel (58, 64) and may be modified by site-directed mutagenesis to be capable of measuring the activity of each mAb individually.

10.5 ADA detection assays

A tiered testing approach will be used to identify and characterize ADAs that may arise (65, 66). Anti-VRC01.23LS, anti-PGT121.414.LS, and anti-PGDM1400LS Ab detection assays (screening, confirmatory, and/or titration) will be performed on serum samples from study participants at indicated timepoints. Samples will be evaluated with a sensitive screening assay in tier 1. Samples showing positive responses in the screening assay will be evaluated in a confirmatory assay of specificity. Specific or tier 2 positive responses will be characterized by titration (tier 3).

10.6 ADA functional assay

A functional ADA assay will be used to characterize any positive activity that is observed in the ADA detection assays. Functional activity will measure a reduction in VRC01.23LS, PGT121.414.LS, and/or PGDM1400LS neutralizing activity against a qualified virus in the TZM-bl assay.

10.7 Ab reaction assays

To investigate Ab reactions, serum samples collected after the onset of reaction may be tested to measure levels of certain markers (eg, tryptase, complement components [C3 and C4], and cytokines). ADA detection and functional assays, as described above, may be performed on serum samples taken prior to the study-product administration associated with the reaction. Refer to the HVTN 143/HPTN 109 SSP for more information.

10.8 HVTN LC assay portfolio

Additional assays may be performed per the HVTN LC assay portfolio, which includes immune assessments, such as those for cellular, humoral, and innate immune responses, and host genetics. The assay portfolio will be updated

periodically to include new assays and adjust qualification levels of existing assays.

10.9 Exploratory studies

Samples may be used for other testing and research related to furthering the understanding of HIV, passive immunity, immunology, Ab-mediated prevention, and clinical trial conduct. In addition, samples may be used to perform additional assays to support standardization and validation of existing or newly developed methods.

10.10 Specimen storage and other use of specimens

The Networks store specimens from all study participants indefinitely unless a participant requests that specimens be destroyed or if destruction or a time limit for storage is required by IRB/EC or RE.

Other use of specimens is defined as studies not covered by the protocol or the ICF for the main study (see Appendix A and Appendix B).

This research may relate to HIV, vaccines, Abs, the immune system, and other diseases. This could include genetic testing and, potentially, genome-wide studies. This research is done only to the extent authorized in each study site's ICF, or as otherwise authorized under applicable law. Other research on specimens ("other use") will occur only after review and approval by the HVTN, the HPTN, the IRB/EC of the researcher requesting the specimens, and IRBs/ECs/REs of the CRS's, if required.

As part of consenting for the study, participants document their initial decision to allow or not allow their specimens to be used in other research, and they may change their decision at any time. The participant's initial decision about other use of their specimens, and any later change to that decision, is recorded by their CRS in a Web-based tool that documents their current decisions for other use of their specimens. The Networks will only allow other research to be done on specimens from participants who allow such use.

CRSs must notify HVTN Regulatory Affairs if institutional or local governmental requirements pose a conflict with or impose restrictions on specimen storage or other use of specimens.

10.11 Biohazard containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be employed by all personnel in the drawing of blood and

shipping and handling of all specimens for this study, as currently recommended by the CDC and the NIH or other applicable agencies.

All dangerous goods materials, including Biological Substances, Category A or Category B, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

11 Safety monitoring and safety review

11.1 Safety monitoring and oversight

11.1.1 HVTN 143/HPTN 109 PSRT

The HVTN 143/HPTN 109 PSRT is composed of the following members:

- DAIDS Medical Officer (MO) representatives
- Protocol Chairs
- Protocol Team Leaders (PTLs)
- Core Medical Monitor
- Regional Medical Liaison (RML)
- Clinical Safety Specialist (CSS)

The clinician members of the HVTN 143/HPTN 109 PSRT are responsible for decisions related to participant safety.

The Protocol Team Clinic Coordinator (CC), Clinical Data Manager (CDM), study-product developer representative, Clinical Trial Manager (CTM), Clinical Research Manager, Network Pharmacist and others may also be included in HVTN 143/HPTN 109 PSRT meetings.

11.1.2 HVTN SMB

The SMB is a multidisciplinary group consisting of biostatisticians, clinicians, and experts in HIV vaccine and drug research that, collectively, has experience in the conduct and monitoring of vaccine, mAb, and other drug trials. Members of the SMB are not directly affiliated with the protocols under review.

The SMB reviews safety data approximately every 4 months. The reviews consist of evaluation of cumulative solicited AEs, unsolicited AEs, laboratory safety data, and individual reports of AEs requiring expedited reporting to DAIDS. The SMB conducts additional special reviews at the request of the HVTN 143/HPTN 109 PSRT.

Study sites will receive SMB summary minutes and are responsible for forwarding them to their IRB/EC and any applicable RE.

11.1.3 Roles and responsibilities in safety monitoring

The roles and responsibilities of the SDMC in relation to safety monitoring include:

- Maintaining a central database management system for clinical data and
- Providing reports of clinical data to appropriate groups such as the HVTN 143/HPTN 109 PSRT and HVTN SMB (see Section 11.1.2).

The roles and responsibilities of the HVTN clinical safety staff (CSS/RML) or HVTN Core designee in relation to safety monitoring include:

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 143/HPTN 109 PSRT AE review criteria (see Section 11.5);
- Notifying CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Sections 11.3 and 11.5);
- Querying CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 143/HPTN 109 PSRT.

11.2 Safety reporting

11.2.1 Submission of safety forms to SDMC.

CRS staff must submit all safety forms (eg, solicited AEs, unsolicited AEs, urinalysis, local lab results, and concomitant medications) before the end of the next business day, excluding federal or bank holidays. The forms should not be held in anticipation of additional information at a later date. If additional information is received at a later date, the forms should be updated and resubmitted before the end of the next business day after receiving the new information. For the case of a longer CRS holiday closure, CRS staff must submit the data by the end of the fifth day (local time) after receiving the information, even if this day is a holiday.

For example, if the CRS becomes aware of an AE on Thursday (day 1, the first day), the CRS must submit the data by the end of the next business day, on Friday (day 2). If there is a longer CRS holiday closure, then this AE must be reported no later than the end of day, Monday (day 5). If Monday is a holiday as well, all safety forms still need to be submitted by the end of Monday (day 5).

11.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation participant who was administered a study product/procedure(s). The AE does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). AEs include both solicited AEs and unsolicited AEs. Solicited AEs are a subset of AEs that are defined per protocol and specifically asked about for 3 full days after each study infusion. Unsolicited AEs include all other AEs that do not fit the definition of a solicited AE. See the SSP for further detail regarding solicited and unsolicited AEs.

The unsolicited AE reporting period for this study comprises the entire study period for each individual participant (from study enrollment until study completion or discontinuation of the study).

All AEs are graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables. Exceptions include:

- Unintentional weight loss is required to be reported as an AE only if it is considered to be potentially deleterious to the participant's health (see HVTN 143/HPTN 109 SSP);

- Infusion-site erythema or redness and infusion-site induration or swelling will not consider surface area and interference with usual social and functional activities, such that:
  - Grade 1 is: 2.5 to < 5 cm in diameter;
  - Grade 2 is: ≥ 5 to < 10 cm in diameter;
  - Grade 3 is: ≥ 10 cm in diameter OR ulceration OR secondary infection OR phlebitis OR sterile abscess OR drainage;
  - Grade 4 is: Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

- Creatinine is required to be reported as an AE only if it is gradable per the increase from local lab ULN/reference-range parameter. Do not grade elevated creatinine based on the change from the baseline parameter.

- Creatinine CL or estimated glomerular filtration rate (eGFR) is required to be reported based only on the reported value or if dialysis is needed. Do not grade creatinine CL or eGFR based on the change from the baseline parameter.

- Ab reactions not represented in the DAIDS table to be graded per the "infusion related reaction" row from the Common Terminology Criteria for Adverse Events (CTCAE) from the DHHS (Version 5.0. Published November 27, 2017, available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [see also HVTN 143/HPTN 109 SSP]).

All AEs are reported to the SDMC on the appropriate CRF. Clinic staff should evaluate every AE to determine if: (1) the AE meets the requirements for expedited reporting to DAIDS (see Section 11.2.3) and (2) the AE meets the criteria for a safety pause/prompt AE review (see Section 11.5).

Sites are expected to notify HVTN clinical safety staff of any serious safety concern requiring their attention (Table 11-2). Telephone numbers and email addresses are found on the protocol home page on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn143-hptn109). Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, clinical safety staff will reply within 1 business day. Serious events that meet pause-rule criteria will be addressed immediately (as outlined in Table 11-2). If email service is not available, the CRS should notify clinical safety staff of the event by telephone, and then submit CRFs.

In addition, CRS investigators are required to submit AE information in accordance with IRB/EC and any applicable RE requirements.

11.2.3 Expedited reporting of AEs to DAIDS

Requirements, definitions, and methods for expedited reporting of AEs are outlined in Version 2.0 (January 2010) of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS expedited adverse event [EAE] Manual), which is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids. The SAE reporting category, as defined in Version 2.0 of DAIDS EAE Manual, will be used for this study.

The internet-based DAIDS Adverse Experience Reporting System (DAERS) must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAE reports may be submitted via the DAIDS EAE form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact CRMSsupport@niaid.nih.gov or from within the DAERS application itself.

For questions about EAE reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

The study products for which expedited reporting are required are:

- VRC01.23LS
- PGT121.414.LS
- PGDM1400LS

While the participant is in the study, from enrollment to the end of trial participation for that participant, the SAE reporting category will be used.

After the end of trial participation for that participant, unless otherwise noted, only suspected unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the DAIDS EAE Manual, must be reported to DAIDS, if the study staff become aware of the events.

The NIAID/DAIDS or designee(s) will prepare and file expedited reports to other appropriate regulatory authorities within the timelines required by pertinent national regulatory agencies.

CRS Investigators of Record (IoRs)/designees will submit AE information and any other relevant safety information to their IRBs/ECs in accordance with IRB/EC requirements.

11.3 Safety reviews

11.3.1 Safety considerations for Part A dose escalation

The HVTN 143/HPTN 109 PSRT will monitor participant safety data throughout the study and as described in this section and in Table 11-1 below. To determine if enrollment may commence in subsequent groups for dose escalation, the HVTN 143/HPTN 109 PSRT will review study safety data and will consider all available safety data on the Abs used in this study, including from ongoing and concurrent clinical trials (eg, VRC615).

11.4 Safety considerations for Part A dose escalation

The trial will begin with enrollment in Part A Group 1 only, then Group 2 only, and then Group 3. Additional participants may be enrolled in each group to ensure the availability of safety data from at least 5 participants in each group.

Enrollment will start with Group 1 and will be restricted to a maximum of 1 participant per day across all participating CRSs until a total of 5 participants have been enrolled. Enrollment will then be held. The HVTN 143/HPTN 109 PSRT will review safety data, as described in Table 11-1. Upon PSRT determination that it is safe to proceed, enrollment in Group 2 will begin.

Enrollment in Group 2 will be restricted to a maximum of 1 participant per day across all participating CRSs until a total of 5 participants have been enrolled. Enrollment will then be held. The HVTN 143/HPTN 109 PSRT will review safety data, as described in Table 11-1. Upon PSRT determination that it is safe to proceed, enrollment in Group 3 will begin.

Enrollment in Group 3 will be restricted to a maximum of 1 participant per day across all participating CRSs until a total of 5 participants have been enrolled.

11.4.1 Safety evaluation for moving from Part A to Part B

The HVTN 143/HPTN 109 PSRT will review safety data, including from Groups 1 through 3, as described in Table 11-1. The HVTN 143/HPTN 109 PSRT will make a decision regarding the appropriateness of allowing enrollment into Part B. If any ≥ Grade 3 AE(s) deemed related to study product are reported in Part A, the HVTN SMB will perform an additional review of this safety data to make the final determination based on safety for proceeding to Part B.

In Part B, Groups 4, 5, 6, 7, and 8 will enroll simultaneously without restrictions.

Table 11-1 Summary of planned safety holds and safety data reviews for dose escalations

Planned safety hold #	Group(s)	Timepoint/data reviewed	Action
1	1	Begins after the fifth participant is enrolled (infused) in Group 1 and the solicited AE assessment data through the day 7 visit is reported. Review of all cumulative safety data available for the 5 participants in Group 1, up to and including the solicited AE assessment data reported at the day 7 visit after the study-product administration.	The PSRT will decide the appropriateness of beginning enrollment in Group 2 based on these safety data.
2	2	Begins after the fifth participant is enrolled (infused) in Group 2 and the solicited AE assessment data through the day 7 visit is reported. Review of all cumulative safety data available, including the first 5 participants in Group 2, up to and including the solicited AE assessment data reported at the day 7 visit after the study-product administration.	The PSRT will decide the appropriateness of beginning enrollment in Group 3 based on these safety data.
3	1-3	Begins after the fifth participant is enrolled (infused) and the solicited AE assessment data through the day 7 visit is reported (5 participants each in Groups 1, 2, and 3). Review of all cumulative safety data available for all participants in Part A (groups 1-3), up to and including the solicited AE assessment data reported at the day 7 visit after the product administration for participants in Group 3.	The PSRT (+/- SMB) will decide the appropriateness of beginning unrestricted enrollment in Part B based on all available safety data from all participants included in Part A.

Note: Additional participants may be enrolled in each group to ensure the availability of safety data from at least 5 participants in each group.

11.5 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all enrollment and study-product administration with the product related to the event that triggered the pause will be held until further notice. The AEs that will lead to a safety pause or prompt HVTN 143/HPTN 109 PSRT AE review are summarized in Table 11-2. Study-product administrations may be suspended for safety concerns other than those described in the table, or before pause rules are met, if, in the judgment of the HVTN 143/HPTN 109 PSRT, participant safety may be threatened. Criteria for an individual participant's departure from the schedule of study-product administrations are listed in Section 7.3.

Table 11-2 AE notification and safety pause/AE review rules

Event and relationship to study products	Severity	CRS action[a]	HVTN LOC action[b]
SAE, related	Grade 5 or Grade 4	Phone immediately, email and submit forms immediately	Immediate pause
SAE, not related	Grade 5	Phone immediately, email and submit forms immediately	Immediate PSRT notification
SAE, related	Grade 3, 2, or 1	Email and submit forms immediately	Immediate PSRT notification and prompt PSRT AE review to consider pause
AE[c], related	Grade 4 or 3	Email and submit forms immediately	Immediate PSRT notification and prompt PSRT AE review to consider pause

[a] Phone numbers and email addresses are found on the protocol home page on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn143-hptn109).

[b] HVTN CSS or RML or other HVTN Core designee

[c] Does not include subjective solicited AEs (infusion-site pain and/or tenderness, fatigue/malaise, myalgia, arthralgia, chills, headache, nausea [unless IV rehydration required], nonexertional dyspnea, generalized pruritus, facial flushing, and unexplained diaphoresis).

For all safety pauses, HVTN LOC notifies the HVTN 143/HPTN 109 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance Team (SPT), and participating CRSs. When an immediate safety pause is triggered, HVTN LOC notifies the SMB.

Once a trial is paused, the HVTN 143/HPTN 109 PSRT reviews safety data and decides whether the pause can be lifted or if permanent discontinuation of study product administration is appropriate, consulting the SMB if necessary. The HVTN LOC notifies the participating CRSs, HVTN Regulatory Affairs, DAIDS PAB, DAIDS RAB, and DAIDS SPT of the decision regarding resumption or discontinuation of study-product administrations. Based on the HVTN 143/HPTN 109 PSRT assessment.

If an immediate HVTN 143/HPTN 109 PSRT notification or prompt HVTN 143/HPTN 109 PSRT AE review is triggered, HVTN Core notifies the HVTN 143/HPTN 109 PSRT as soon as possible during working hours (local time) or, if the information was received during off-hours, by the morning of the next workday. If a prompt HVTN 143/HPTN 109 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

The HVTN and HPTN require that each CRS submit to its IRB/EC and any applicable RE protocol-related safety information (such as IND safety reports, notification of study-product holds due to the pause rules, unanticipated problems involving risks to participants or others, and notification of other unplanned safety pauses). CRSs must also follow all applicable RE reporting requirements.

In addition, all other AEs are reviewed routinely by the HVTN 143/HPTN 109 PSRT (see Section 11.6.2).

11.6 Review of cumulative safety data

Routine safety review occurs at the start of enrollment and then throughout the study.

Reviews proceed from a standardized set of protocol-specific safety data reports. These reports are produced by the SDMC and include queries to the CRSs. Events are tracked by internal reports until resolution.

11.6.1 Daily review

Daily safety reviews are routinely conducted by HVTN Core for events requiring expedited reporting to DAIDS, and events that meet safety pause criteria or prompt HVTN 143/HPTN 109 PSRT AE review criteria.

11.6.2 Weekly review

During the study-product administration phase of the trial, the HVTN 143/HPTN 109 PSRT reviews clinical safety reports on a weekly basis and conducts calls to review the data, as appropriate. Following the visit 8 weeks post–final study-product administration, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 143/HPTN 109 PSRT. HVTN LOC reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the CRS CC for verification.

11.7 Study termination

NIAID reserves the right to terminate or curtail a clinical study for any reason, including but not limited to the following (reference: https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-012.html):

- Risk to participant safety
- The scientific question is no longer relevant or the objectives will not be met (ie, slow accrual)
- Failure to comply with GCP, all applicable regulations, or terms and conditions of award
- Occurrence of unforeseen drug safety issues or data from preclinical studies indicate a presence of unanticipated toxicity

- Risks that cannot be adequately quantified
- Ethical concerns raised by the local community or local medical care/healthcare authorities
- Failure to remedy deficiencies identified through site monitoring
- Substandard data
- Reaching a major study endpoint substantially before schedule with persuasive statistical significance.

This study may also be terminated early by the determination of the HVTN 143/HPTN 109 PSRT, a pertinent national regulatory authority, NIH, the Office for Human Research Protections (OHRP), or study-product developer(s). In addition, the conduct of this study at an individual CRS may be terminated by the determination of the IRB/EC and any applicable RE.

12 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with the principles of GCP (ICH E6[R2]), and according to DAIDS, HVTN, and HPTN policies and procedures as specified in the network-specific MOP, DAIDS Clinical Research Policies, and Standard Procedures Documents, including procedures for the following:

- Protocol registration, activation, and implementation;
- Informed consent, screening, and enrollment;
- Study-participant reimbursement;
- Clinical and safety assessments;
- Safety monitoring and reporting;
- Data collection, documentation, transfer, and storage;
- Participant confidentiality;
- Study follow-up and close-out;
- Quality control;
- Protocol monitoring (on-site or remote) and compliance;
- Advocacy and assistance to participants regarding negative social impacts associated with the trial;
- Risk-reduction counseling;
- Specimen collection, processing, and analysis;
- Exploratory and ancillary studies and substudies, and
- Destruction of specimens.

DAIDS, HVTN, and HPTN policies and procedures are available for review by any IRB/EC/RE upon request.

Any policies or procedures that vary from DAIDS, HVTN, or HPTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the HVTN 143/HPTN 109 SSP.

12.1 Social impacts

It is possible that participants' involvement in the study could result in social impacts. Social harms are negative social impact events and social benefits are positive social impact events that a participant reports as affecting them as a result of being involved in a research study. It is not the researcher's opinion of how they perceive an event has affected a participant. For example, a participant's involvement in the study could become known to others, and a social harm may result (eg, participants could be perceived as having HIV or as having a high likelihood of acquiring HIV). Participants could be treated unfairly or could have problems being accepted by their families and/or communities. Alternatively, a social benefit may result (eg, a participant could feel good helping others).

Social impacts will be collected and reported on CRFs during scheduled visits (see Appendix H and Appendix I). Social harms are tabulated by the SDMC and are subjected to descriptive analysis. The goal is to reduce their incidence and enhance the ability of study staff to mitigate them when possible. Summary tables of social impact events will be generated weekly and made available for review by the protocol chairs, PTL, and the designated NIAID representative. A social harm that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to their individual requirements.

In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety and well-being of the participant. If CRS staff have questions regarding ways to assist a participant dealing with a social impact, a designated NIAID or Network Core representative can be contacted. While maintaining participant confidentiality, study sites may engage their CAB in exploring the social context surrounding instances of social harms to minimize the potential occurrence of such an impact.

12.2 Emergency communication with study participants

As in all clinical research, this study may generate a need to reach participants quickly to avoid imminent harm, or to report study findings that may otherwise concern their health or welfare.

When such communication is needed, the CRS will request that its IRB/EC and any applicable RE expedite review of the message. If this review cannot be completed in a timeframe consistent with the urgency of the required communication, the CRS can contact the participant without IRB/EC approval if such communication is necessary to avoid imminent harm to the study participant. The CRS must notify the IRB/EC and any applicable RE of the matter as soon as possible.

13 Version history

The Protocol Team may modify the original version of the protocol. Modifications are made to Network protocols via clarification memos, letters of amendment, or full protocol amendments.

The version history of, and modifications to, Protocol HVTN 143/HPTN 109 are described below.

Protocol history and modifications

Date: June 07, 2023

Protocol version:1.0
Protocol modification:

Original protocol

14 Document references (other than literature citations)

Other documents referred to in this protocol, and containing information relevant to the conduct of this study, include:

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current Centers for Disease Control (CDC) Guidelines.
  - Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf.
  - Revised Guidelines for HIV Counseling, Testing, and Referral. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures
- Division of AIDS Protocol Registration Manual. Available at https://www.niaid.nih.gov/sites/default/files/prmanual.pdf
- Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, July 2017. Available at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids
- Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Published November 27, 2017. Available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HPTN Certificate of Confidentiality.
- HVTN 143/HPTN 109 Special Instructions. Accessible through the HVTN protocol-specific website.

- HVTN 143/HPTN 109 Study Specific Procedures. Accessible through the HVTN protocol-specific website.

- HVTN 143/HPTN 109 Site Lab Instructions. Accessible through the HVTN protocol-specific website.

- Ab Manual of Operations. Accessible through the HVTN website.

- Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at https://www.iata.org/publications/dgr/Pages/index.aspx

- Lab assay algorithm (available upon request)

- International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6, Guideline for Good Clinical Practice: Section 4.8, Informed consent of trial subjects. Available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

- Participants' Bill of Rights and Responsibilities. Accessible through the HVTN website.

- National Institutes of Health (NIH) Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research. Available at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html

- Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, July 2008.

- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at https://www.niaid.nih.gov/sites/default/files/score-source-documentation-requirements.pdf

- Title 21, Code of Federal Regulations, Part 50. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

- Title 45, Code of Federal Regulations, Part 46. Available at https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

- The Protection of Personal Information Act (POPIA, South Africa, 2013). Available at https://www.gov.za/sites/default/files/gcis_document/201409/3706726-11act4of2013protectionofpersonalinforcorrect.pdf

See Section 16 for literature cited in the background and statistics sections of this protocol.

15 Acronyms and abbreviations

λz	terminal elimination rate constant
Ab	antibody
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AFAB	assigned female sex at birth
Alk Phos	alkaline phosphatase
ALT	alanine aminotransferase
AMAB	assigned male sex at birth
AMP	antibody-mediated prevention
ANOVA	analysis of variance
AoU	Assessment of Understanding
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATI	analytical treatment interruption
AUC	area under the curve
AUC-MB	area under the magnitude-breadth curve
BAMA	binding antibody multiplex assay
β-HCG	beta human chorionic gonadotropin
BIDMC	Beth Israel Deaconess Medical Center
bnAb	broadly neutralizing antibody
CAB	Community Advisory Board
CAVD	Collaboration for AIDS Vaccine Discovery
CBC	complete blood count
CC	Clinic Coordinator
CD4bs	CD4 binding site
CDC	US Centers for Disease Control and Prevention
CDM	Clinical Data Manager
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CAVD	Collaboration for AIDS Vaccine Discovery
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CRF	case report form

CRPMC	NIAID Clinical Research Products Management Center
CRS	clinical research site
CSR	central specimen repository
CSS	Clinical Safety Specialist
CTCAE	Common Terminology Criteria for Adverse Events
CTM	Clinical Trials Manager
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	The Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
EAE	expedited adverse event
EC	Ethics Committee
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
Env	HIV envelope protein
Fc	Fragment crystallizable
FcRn	neonatal Fc receptor
FDA	US Food and Drug Administration
FIH	first-in-human
FR3	Framework 3
Fred Hutch	Fred Hutchinson Cancer Center
GCP	Good Clinical Practice
GEE	generalized estimating equation
GLP	Good Laboratory Practice
GPL	immunoglobulin G phospholipid
GPP	Good Participatory Practices
HBsAg	hepatitis B surface antigen
HC	heavy chain
HCV	hepatitis C virus
HEp-2	human epithelial cell line
HPTN	HIV Prevention Trials Network
HSML-NICD	HIV Seromolecular Laboratory – National Institute for Communicable Diseases
HSV	herpes simplex virus type 2
HVTN	HIV Vaccine Trials Network
IAS-USA	International Antiviral Society – USA
IAVI	International AIDS Vaccine Initiative
IB	Investigator's Brochure
IC	inhibitory concentration
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IND	Investigational New Drug
IoR	Investigator of Record
IP	investigational product
IRB	Institutional Review Board
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous
KI	knock-in
L	leucine
LC	HVTN Laboratory Center
LOC	HVTN Leadership and Operations Center
mAb	monoclonal antibody
MAR	missing at random
MB	magnitude breadth
MCAR	missing completely at random
MITT	modified intent-to-treat
MO	DAIDS Medical Officer
MOP	Manual of Operations
MTD	maximum tolerated dose
nAb	neutralizing antibody
NAEPP	National Asthma Education and Prevention Program
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NIH	US National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drugs
OD	optimal density
OHRP	US Office for Human Research Protections
PAB	DAIDS Pharmaceutical Affairs Branch
PCR	polymerase chain reaction
PD	pharmacodynamics
PI	Principal Investigator
PID	pelvic inflammatory disease
PK	pharmacokinetics
POPIA	Protection of Personal Information Act
popPK	population pharmacokinetic
PP	per-protocol

PrEP	pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
PTL	Protocol Team Leader
RAB	DAIDS Regulatory Affairs Branch
RE	Regulatory Entity
RML	Regional Medical Liaison
RSC	DAIDS Regulatory Support Center
RSV	respiratory syncytial virus
S	serine
SAE	serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SAIL-NICD	South African Immunology Laboratory – National Institute for Communicable Diseases
SAP	Statistical Analysis Plan
SC	subcutaneous
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SD	standard deviation
SDMC	HVTN Statistical and Data Management Center
SHIV	simian-human immunodeficiency virus
SICF	sample informed consent form
SMB	Safety Monitoring Board
SOP	standard operating procedures
SPT	DAIDS Safety and Pharmacovigilance Team
SSP	study-specific procedures
SST	serum-separating tube
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
t1/2	half-life
TB	tuberculosis
TCR	tissue cross-reactivity
Tmax	time to maximum concentration
ULN	upper limit of normal
USP	United States Pharmacopeia
UW-VSL	University of Washington Virology Specialty Laboratory
VCMP	Vaccine Clinical Materials Program
Vd	volume of distribution
VRC	Dale and Betty Bumpers Vaccine Research Center (NIAID)
VRP	Vaccine Research Program
VTRB	Vaccine Translational Research Branch

w/v	weight per volume
WBC	white blood cell

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Appendix A Sample informed consent form for Part A

Title: A phase 1 clinical trial to evaluate the safety, tolerability, and pharmacokinetics of monoclonal antibodies VRC01.23LS, PGT121.414.LS and PGDM1400LS administered via intravenous infusion in adults without HIV

Protocol number: HVTN 143/HPTN 109

Site: [Insert site name]

Thank you for your interest in our research study. Please read this consent form or ask someone to read it to you. If you decide to join the study, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

Key Information

These are some of the things you should know about this study:

- The purpose of this part of the study is to understand how the body's immune system responds to a new lab-made antibody against HIV. Antibodies are proteins made by the body as one way to respond to or fight infection.
- We also want to see if the antibody is safe to give to people and does not make them too uncomfortable.
- You will be in the study for about 6 months. You will get the study antibody in a vein by IV infusion at one visit. This is also known as getting a drip.
- We will collect blood samples from you at each study visit to see how your body responds to the study antibody, and to measure how much of the study antibody is in your blood.
- We will test you for HIV and other sexually transmitted infections (STIs) and pregnancy (if applicable). We will ask you to complete questionnaires and you will have physical exams.
- Overall, the general risks of antibodies are mild, and can include fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, fatigue, flushing, diarrhea, trouble breathing, high or low blood pressure, itchiness, and rash. There may be other side effects that we don't yet know about, even serious ones. Because one of the study antibodies is being given to people for the first time in another study, we do not know what all of the risks may be. We think that the risks will be similar to these general risks.

- There is no direct benefit to you from being in the study.
- It is your choice whether or not to take part in this study. You do not have to take part in the study and you are free to stop at any time.
- The rest of this form provides a more complete description of this study. Please read it carefully.

About the study

The HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), and [Insert site name] are doing a study to test a combination of different antibodies against HIV. HIV is the virus that causes AIDS. Antibodies are made by the body as one way to respond to or fight infection. Researchers can also make antibodies in laboratories and give them to people by IV drip into a vein. We will tell you more about this procedure below. Antibodies have been used successfully to prevent or treat other health problems, such as COVID-19 caused by SARS-CoV-2 virus, and respiratory infections in babies caused by respiratory syncytial virus (RSV).

About 77 people will take part in this study at multiple clinics. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

There are 2 parts of this study: Part A and Part B. About 15 people will take part in Part A of this study to test one study antibody at different doses. After we see the results from Part A, we will decide whether or not to do Part B of the study, that will test a combination of 3 antibodies at different doses. If we decide to do Part B, 62 more people will join.

You are being invited to join Part A of the study.

1. **We are doing this part of the study to answer several questions.**
   - Is the new study antibody safe to give to people by itself at different doses?
   - Are people able to take the new study antibody without becoming too uncomfortable?
   - How do people's immune systems respond to the new study antibody? (Your immune system protects you from disease.)
   - How much of the antibody remains in the body as time passes?
2. **The study antibody cannot give you HIV.**

   The study antibody is not made from actual HIV. It is impossible for the study antibody to give you HIV. Also, it cannot cause you to give HIV to someone else.

We do not know if the study antibody will decrease, increase, or not change your likelihood of getting HIV if you are exposed to the virus.

3. This study antibody is experimental.

The study antibody is called VRC01.23LS. From here on, we will call it the "study antibody." It is an experimental product for HIV prevention. That means we do not know if it will be safe to use in people or if it will work to prevent HIV. This antibody is used only in research studies.

The antibody was developed by the Dale and Betty Bumpers Vaccine Research Center (VRC) at the US National Institutes of Health (NIH). In this study, the antibody is provided by the NIH.

VRC01LS is a previous version (or "parent") of VRC01.23LS, the product we will use in this study. VRC01LS has been tested in 5 other studies. So far, 112 participants including children have received 1 or more doses of VRC01LS with an IV drip or under their skin. VRC01LS has been well-tolerated in adults and children and there have been no serious health concerns reported. The study antibody is different from this "parent" because of 2 changes made to its structure. We think these changes will help block HIV from attaching to cells in your immune system, called CD4-T cells, that usually fight HIV if a person is ever exposed to it, and will make the study antibody last longer in the body. Otherwise the two antibodies are the same.

Lab-made antibodies given to a person usually do not last in the body more than a few months. One of the goals of this study is to see how long this antibody will stay in the body. We don't know yet how long it will last, but we think it may be several months.

Risks of the study antibody:

Because the study antibody is being given to people for the first time in another ongoing study, we do not know what all of the risks may be. We think that the risks will be similar to the risks seen with the earlier "parent" version of the study antibody called VRC01LS. In studies of the parent antibody, some participants said that they felt mild pain and tenderness where they got the IV drip, but most participants described this as mild and could continue with their daily activities. The other side effects that were reported were the same as the general risks of antibodies described below, and people described them as mild to moderate. Overall, safety data from the other studies have found that VRC01LS is safe and does not cause serious health problems when given at the same doses that will be used in this study.

This section lists the side effects we know about. There may be others that we don't yet know about, even serious ones. We will tell you if we learn about any new side effects.

General risks of antibodies:

Other kinds of antibodies used for other health problems have caused side effects within the first 24 hours of getting the antibody. Those antibodies have caused fever, chills, itchiness, rash, hives, redness in the cheeks and neck, lip or face swelling, nausea, vomiting, pain, diarrhea, fatigue, headache, dizziness, shaking, trouble breathing, high or low blood pressure, racing heartbeat, and chest pain. Some of these reactions have been seen in the studies using earlier versions of the study antibody, but they were mild and did not affect most participants' daily lives.

These reactions may be related to how an antibody is made, what it targets, or how fast the IV drip is given. Sometimes, the side effects include reactions at the place where the IV drip was given.

Joining the study

4. **It is completely up to you whether or not to join the study.**

   Take your time in deciding. If it helps, talk to people you trust, such as your doctor, friends, or family. If you decide not to join this study, or if you leave it after you have joined, your other care at this clinic and the benefits or rights you would normally have will not be affected.

   If you join this study, you may not be allowed to join some other HIV prevention studies now or in the future. You cannot be in this study while you are in another study where you get a study product. Being in more than 1 study may not be safe. We check to make sure that you are not in more than 1 study by taking your fingerprint on an electronic system. This information is accessed by only a few members of the study team using a secure password.

   You should not donate blood or tissue during the study.

   If you choose not to join this study, you may be able to join another study.

Site: Remove item 5 if you use a separate screening consent that covers these procedures.

5. **If you want to join the study, we will screen you to see if you are eligible.**

   Screening involves a physical exam, HIV test, and health history. A physical exam may include, but is not limited to:

   - Checking your weight, temperature, and blood pressure
   - Looking in your mouth and throat
   - Checking your veins to see how easy it might be to start an infusion

- Looking at your skin
- Listening to your heart and lungs
- Feeling your abdomen (stomach and liver)
- Asking you about vaccines you have gotten recently

We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are doing. We will ask you about medications you are taking. We will ask you about behaviors that might make you more likely to acquire HIV.

If you are capable of becoming pregnant, we will test you for pregnancy. If you have had your uterus or ovaries removed (a hysterectomy or oophorectomy), and this is verified by medical records, you are not required to have a pregnancy test.

We will review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

Site: adapt the following section so it is applicable to the care available at your site

6. **If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here for free.**

   For the care that we cannot give, we will explain how we will help you get care elsewhere. For health problems that are unrelated to the study, we will not pay for care.

7. **If you could become pregnant, you must agree to use contraception to join this study.**

Site: If you want to include Appendix C, Approved contraception methods (for sample informed consent form), in this consent form, paste it below and delete paragraph below.

You should not become pregnant during the study because we do not know how the study antibody could affect a developing baby. You must agree to use effective contraception from 21 days before your first IV drip until 8 weeks after your last clinic visit. We will talk to you about effective contraception methods. They are listed on a handout that we will give to you.

You also should not begin the process to have your eggs collected from 21 days before your first IV drip until 8 weeks after your last clinic visit. If this is something you are considering, please discuss it with your study doctor and your fertility specialist.

Being in the study

If you meet the study requirements and want to join, here is what will happen:

8. **You will come to the clinic for scheduled visits about 7 times over 6 months.**

Site: Insert range of visit lengths, noting the different visit lengths for infusion visits and other follow-up visits.

Most of the visits will be 1-2 months apart. After you get the study antibody, we will ask you to come to the clinic for follow-up visits about 3 days and 6 days after the IV drip to collect your blood sample. We will do this so that we can look at how your body responds to the study product. Visits where you get an IV drip can last from [#] to [#] hours. Other visits will be from [#] to [#] hours.

You may have to come for more visits if you have a lab or health issue.

We may contact you after the study ends (for example, to tell you about the study results).

9. **We will give you [Site: Insert compensation] for each study visit you complete.**

This amount is to cover the costs of [Site: Insert text]

Site: Insert any costs to participants (eg, contraception costs for participants who could become pregnant).

You do not have to pay anything to be in this study.

10. **We will give you the study antibody by IV drip at your enrollment visit.**

We will use a sterile needle to place a small plastic tube into a vein in your arm or hand. The small plastic tube is connected to a small bag of fluid that contains the study antibody. A pump controls how fast the fluid drips from the bag, through the tube, and into your vein. The IV drip will take about 1 hour.

If you have any symptoms while you are getting the study antibody, tell the study staff. Slowing or stopping the flow rate may help improve the symptoms.

11. **We will give you the study antibody at 1 visit.**

You will be in 1 of 3 groups. All groups will get the study antibody, but at different doses. You will get 1 IV drip during the study as shown in the table below.

People in Group 1 will be enrolled first and given the study antibody. When all 5 participants in Group 1 have gotten the study antibody, the safety information will

be reviewed. If there are no safety concerns for Group 1, enrollment will begin for Group 2. Five more people will be enrolled in Group 2. If there are no safety concerns for Group 2, Group 3 will begin. Five more people will be enrolled in Group 3. You will not be able to choose which group you are in. The assignment will depend on which group is available at the time you join.

The doses of the study antibody will be adjusted for your body weight. We will weigh you to determine the correct amount before giving you the IV drip.

Infusion schedule:				
Group	**Number of participants**	**Dose**	**How it is given**	**Enrollment Visit**
1	5	Lower	IV drip	VRC01.23LS
2	5	Medium	IV drip	VRC01.23LS
3	5	Higher	IV drip	VRC01.23LS

You will have to wait in the clinic for about 1 hour after the IV drip to see if there are any problems. We will collect a blood sample about 1 hour after the drip is finished. Then, for that night and for 3 more days, you will need to keep track in a diary of how you are feeling and if you have any symptoms. *Site: Customize the next sentence based on how you collect reactogenicity information.* We will review the diary with you during the visits after you get the IV drip. You will turn in the diary by the day 6 visit. Contact the clinic staff if you have any issues or concerns after getting the IV drip. If you have a problem, we will continue to check on you until it goes away.

12. In addition to giving you the study antibody, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid HIV
- Do physical exams
- Do pregnancy tests if you could become pregnant
- Ask questions about your health, including medications you may be taking, including pre-exposure prophylaxis (PrEP)
- Ask questions about any personal problems or benefits you may experience from being in the study
- Ask questions about your experience getting infusions
- Take urine and blood samples.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 25 mL and 97 mL (a little less than 2 tablespoons to

a little less than 1/2 cup). Your body will make new blood to replace the blood we take out.

Site: You may want to add a sentence to the end of the previous paragraph contextualizing the blood volumes described (eg, "To compare, people who donate blood in the US can give a total of about 500 mL in an 8-week period."). Modify the example for cultural relevance and alter blood volumes as necessary.

Site: Insert Appendix E, Table of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.

We will be looking for side effects. We will review the results of these procedures and tests with you at your next visit, or sooner if necessary. If any of the results are important to your health, we will tell you.

13. Getting approved vaccines while you are in this study is allowed.

If you are planning to get any approved vaccines, please tell us so that we can schedule your study visits with this in mind. To be sure that we can answer the study questions, we will not give the study infusion within 7 days before or after you get a COVID-19 vaccine. We will wait 2-4 weeks before or after you get a vaccine for MPOX.

14. We will counsel you about protecting yourself from HIV.

We will ask you personal questions about factors that may make you more likely to acquire HIV, such as sexual behavior, alcohol, and drug use. We will talk with you about ways to keep your likelihood of acquiring HIV low.

15. We will test your samples.

We will send your samples (without your name) to labs approved by the HVTN and HPTN for this study, which are located in the United States and South Africa. In rare cases, some of your samples may be sent to labs approved by the HVTN and HPTN in other countries for research related to this study.

Researchers will look at how your body, including your immune system, responds to the study vaccine. They may also look at how your body responds to infections and other vaccines. They may use your samples to improve or create new lab tests.

Researchers may also do genetic testing related to this study on your samples. Your genes are passed to you from your birth parents. They affect how you look and how your body works. The genetic testing will only involve some of your genes, not all of your genes (your genome). It will involve genes related to the immune system and HIV.

If you get HIV, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and how the virus is impacted by the study vaccine.

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

These tests done on your samples are for research purposes, not to check your health. The labs will not give the results to you or this clinic because their tests are not approved for use in making health care decisions. These labs are only approved to do research tests.

When your samples are no longer needed for this study, the HVTN and HPTN will continue to store them.

16. We will do our best to protect your private information.

Your study records and samples will be kept in a secure location. We will label all of your samples and most of your records with a code number, not your name or other personal information. However, it is possible to identify you, if necessary. We will not share your name with the lab that does the tests on your samples, or with anyone else who does not need to know your name.

Clinic staff will have access to your study records. Your records may also be reviewed by groups who watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health (NIH)/Division of AIDS (DAIDS), and its study monitors,
- Any regulatory agency that reviews clinical trials,
- [Insert name of local IRB/EC] ,
- South African Health Products Regulatory Authority (SAHPRA)
- [Insert name of any other local and/or national regulatory authority as appropriate]
- The HVTN, HPTN, and the people who work for them,
- The Safety Monitoring Board, and
- The US Office for Human Research Protections (OHRP).

All reviewers will take steps to keep your records private.

We cannot guarantee absolute privacy. If you are found to have a medical condition that we are required to report by law, then some of your information may be shared. At this clinic, we have to report the following information:

Site: Include any public health or legal reporting requirements,including SARS-CoV-2/COVID-19. Bulleted examples should include all appropriate cases (reportable communicable disease, risk of harm to self or others, etc.). If your site does not have public health or legal reporting requirements, you may delete the last sentence in the paragraph above, along with the bullets below.

- [Item 1]
- [Item 2]
- [Item 3]

In addition, the Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing, and sharing another entity's personal information by holding them accountable should they abuse or compromise your personal information in any way.

The results of this study may be published. No publication will use your name or identify you personally.

We may share information from the study with other researchers. We will not share your name or information that can identify you.

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

Leaving the study

17. We may stop your infusions even if you want to stay in the study and even if you were scheduled for more infusions.

If you become pregnant, we will encourage you to stay in the study, but it will be your choice. You may complete study procedures unless there is a medical reason not to. If you leave the study while you are still pregnant, we will contact you after your due date to ask some questions about your pregnancy and delivery if you agree.

If you acquire HIV, we will also take fewer samples, and we will help you get care and support. We will encourage you to stay in the study if you choose. We will counsel you about having HIV and about telling your partner(s). *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

18. We may take you out of the study at any time.

We may take you out of the study if:

- You do not follow instructions,
- We think that staying in the study might harm you,
- The study is stopped for any reason.

19. Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

Previously collected information about you will remain in the study records and will be included in the analysis of results. Your information cannot be removed from the study records.

We may ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We may also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Other Risks

20. There are other risks to being in this study.

This section describes the other risks and restrictions we know about. There may also be unknown risks, even serious ones. We will tell you if we learn anything new that may affect your willingness to stay in the study.

Risks of abnormal laboratory results

Minor changes in test results occasionally happen. This means that the test results can be abnormal even if you have no illness or problem. If this happens, we may ask you to come back to the clinic to be retested. This may cause you to worry, and it may be inconvenient to come back to the clinic. If we determine you have a health problem, we will provide care or help you get the care you need.

Risks of giving blood:

Giving blood can cause bruising, pain, fainting, soreness, redness, swelling, itching, bleeding, and infection (rarely). Giving blood can cause a low blood-cell count (anemia), making you feel tired.

Risks of getting an IV drip:

Getting an IV may cause stinging, discomfort, pain, soreness, redness, bruising, itching, rash, and swelling where the needle goes into the skin. Rarely, needle sticks can result in a blood clot or infection.

Personal problems/discrimination:

Some people who join HVTN and HPTN studies report personal problems or discrimination because of joining an HIV prevention study. Family or friends may worry, get upset or angry, or assume that you have HIV or are likely to acquire HIV and treat you unfairly as a result. Rarely, a person has lost a job because the study took too much time away from work or because their employer thought they had HIV.

HIV testing:

HIV antibody tests are the usual way to test for HIV. We are still learning how HIV tests perform when people are given study antibodies. We have used several common HIV antibody tests to test samples of blood containing antibodies that are similar to the study antibody. We found that very high levels of these similar antibodies can cause positive or uncertain results on some HIV tests. You may have such high levels for a short time after you get the study antibody. This means that for a few days after getting the study antibody, some HIV tests might say you have HIV, even if you don't.

For this reason, you should plan to get HIV tests only at this clinic during the study. Our tests can truly detect HIV. They can also tell if someone does not have HIV. We do not expect you to have any problems with HIV testing after the study ends.

Embarrassment/anxiety:

You may feel embarrassed when we ask questions about behaviours that may make you more likely to acquire HIV, such as having sex and using drugs. Also, waiting for your HIV test results or other health test results could make you feel anxious. You could feel worried if your test results show that you have HIV. If you feel embarrassed or anxious, please tell us and we will try to help you.

Risks of disclosure of your personal information:

We will take several steps to protect your personal information. Although the risk is very low, it is possible that your personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like.

Risks of genetic testing:

It is unlikely, but the genetic tests done on your samples could show that you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

Unknown risks:

We do not know if the study antibody will increase, decrease, or not change your likelihood of getting HIV if you are exposed. If you get HIV, we do not know how the study antibody might affect HIV or how long it takes to develop AIDS.

We do not know if getting this study antibody will affect how you respond to any future approved HIV antibody or vaccine. Currently, no HIV antibody or vaccine has been approved for use.

We do not know how the study antibody will affect a pregnant participant or a developing baby.

Benefits

21. The study may not benefit you.

We do not expect the study antibody to benefit you in any way. However, being in the study might still help you in some ways. The counseling that you get as part of the study may help you to avoid getting HIV. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about.

When asked, some HIV vaccine trial participants stated that participating made them feel good about helping others and increased their knowledge about HIV.

This study may help in the search for an antibody or vaccine to prevent HIV. However, if the study antibody or a vaccine later become approved and sold, there are no plans to share any money with you.

Your rights and responsibilities

22. If you join the study, you have rights and responsibilities.

You have many rights that we will respect. You also have responsibilities. We list these in the Bill of Rights and Responsibilities for HIV Research. We will give you a copy of it.

Injuries

Sites: Approval from HVTN Regulatory Affairs (at vtn.core.reg@hvtn.org) is needed for any change (other than those that the instructions specifically request or those

previously approved by HVTN Regulatory Affairs) to the boxed text. You can remove the box around the text.

23. If you get sick or injured during the study, contact us immediately.

Your health is important to us. *(Sites: adjust the following 2 sentences if applicable to the care available at your site)* We will tell you about the care that we can give here. For the care that we cannot provide, we will explain how we will help you get care elsewhere.

If you become sick or injured in this study, the HVTN has a process to decide if it is related to the study product and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries.

In this study, our clinic has insurance to cover your medical treatment in the case of a study-related injury. We will follow the Association of the British Pharmaceutical Industry guidelines for payment of study-related injury. We can give you a copy of these guidelines. In rare cases, the insurance funds may not be enough.

The HVTN has limited funds to pay medical costs that it determines are reasonable. If the injury is not study related, then you and/or your health insurance will be responsible for treatment costs.

Some injuries are not physical. For example, you might be harmed emotionally by being in an HIV prevention study, or you might lose wages because you cannot go to work. However, there are no funds to pay for these kinds of injuries, even if they are study related.

You may disagree with the decision about whether your injury is study related. If you wish, the HVTN will ask independent experts to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

24. If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact
[name or title and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact
[name or title and telephone number of the investigator or other study staff].

This study has been reviewed and approved by a committee called the
[name of local IRB/EC]. If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study,

contact [name or title and telephone number of person on IRB/EC] at the committee.

The study has been structured in accordance with the Declaration of Helsinki (last updated October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants, *the Ethics in Health Research: Principles, Structures and Processes Second Edition 2015, and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa*. We can provide you with copies of these guidelines if you wish to review them.

If you want to leave this study, contact
[name or title and telephone number of the investigator or other study staff].

You can reach a study staff member 24 hours a day at [telephone number].

If you have questions about this trial, you should first discuss them with your doctor or the Ethics Committee (contact details as provided on this form). After you have consulted your doctor or the Ethics Committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park
Building A
402 Kirkness Street
Arcadia, Pretoria
0083
E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

Your permissions and signature

25. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.
- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)	Participant's signature or mark	Date	Time

Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the entire discussion of this consent form.

Appendix B Sample informed consent form for Part B

Title: A phase 1 clinical trial to evaluate the safety, tolerability, and pharmacokinetics of monoclonal antibodies VRC01.23LS, PGT121.414.LS and PGDM1400LS administered via intravenous infusion in adults without HIV

Protocol number: HVTN 143/HPTN 109

Site: [Insert site name]

Thank you for your interest in our research study. Please read this consent form or ask someone to read it to you. If you decide to join the study, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

Key Information

These are some of the things you should know about this study:

- The purpose of this part of the study is to understand how the body's immune system responds to lab-made antibodies against HIV when they are given in combination at different doses. Antibodies are proteins made by the body as one way to respond to or fight infection.

- We also want to see if the antibodies are safe to give to people and do not make them too uncomfortable.

- You will be in the study for about 12 months. You will get the study antibodies in a vein by IV infusion at 2 visits. This is also known as getting a drip.

- We will collect blood samples from you at each study visit to see how your body responds to the study antibodies and to measure how much of the study antibodies is in your blood.

- We will test you for HIV and other sexually transmitted infections (STIs) and pregnancy (if applicable). We will ask you to complete questionnaires and you will have physical exams.

- Overall, the general risks of antibodies are mild, and can include fever, chills, shaking, nausea, vomiting, pain, diarrhea, headache, dizziness, fatigue, flushing, trouble breathing, high or low blood pressure, itchiness, and rash. There may be other side effects that we don't yet know about, even serious ones. Because one of the study antibodies is being given to people for the first time in another study, and this is the first time this combination of antibodies

is being given to people, we do not know what all of the risks may be. We think that the risks will be similar to the general risks.

- There is no direct benefit to you from being in the study.
- It is your choice whether to take part in this study. You do not have to take part in the study and you are free to stop at any time.
- The rest of this form provides a more complete description of this study. Please read it carefully.

About the study

The HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), and [Insert site name] are doing a study to test a combination of antibodies against HIV. HIV is the virus that causes AIDS. Antibodies are made by the body as one way to respond to or fight infection. Researchers can also make antibodies in laboratories and give them to people by IV drip into a vein or under the skin. We will tell you more about this procedure below. Antibodies have been used successfully to prevent or treat other health problems, such as COVID-19 caused by the SARS-CoV-2 virus, and respiratory infections in babies caused by respiratory syncytial virus (RSV).

About 77 people will take part in this study at multiple sites. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

There are 2 parts of this study. Part A has already been completed. In Part A, we gave different doses of one of the study antibodies to 15 people. People in Part A got the study antibody once. The results of Part A show that it is safe to move ahead with Part B of the study. In Part B, we will give about 62 more people a combination of 3 study antibodies, including the one tested in Part A.

You are being invited to join Part B of the study.

1. **We are doing this part of the study to answer several questions:**

- Are the study antibodies safe to give to people together at different doses?
- Are people able to take the study antibodies without becoming too uncomfortable?
- How do people's immune systems respond to the study antibodies? (Your immune system protects you from disease.)
- How much of the antibodies remain in the body as time passes?

2. The study antibodies cannot give you HIV.

The study antibodies are not made from actual HIV. It is impossible for the study antibodies to give you HIV. Also, they cannot cause you to give HIV to someone else. We do not know if the study antibodies will decrease, increase, or not change your likelihood of getting HIV if you are exposed to the virus.

3. These study antibodies are experimental.

The study antibodies are called VRC01.23LS, PGT121.414.LS, and PGDM1400LS. They are experimental products for HIV prevention. That means we do not know if they will be safe to use in people or if they will work to prevent HIV. These antibodies are used only in research studies. When we talk about them together, we call them the "study products" or the "study antibodies".

The VRC01.23LS study antibody was developed by the Dale and Betty Bumpers Vaccine Research Center (VRC) at the US National Institutes of Health (NIH). PGT121.414LS was developed by Just Biotherapeutics together with the Collaboration for AIDS Vaccine Discovery (CAVD). PDGM1400LS was also developed by the VRC. The study antibodies for this study are being provided by the NIH.

The VRC01.23LS study antibody has been given to the 15 people who were enrolled in Part A. A review of the safety information from these participants shows that it is safe to continue with Part B of the study.

VRC01LS is a previous version (or "parent") of VRC01.23LS, the product we will use in this study. VRC01LS has been tested in 5 other studies. So far, 112 participants including children have received 1 or more doses of VRC01LS with an IV drip or under their skin. VRC01LS has been well-tolerated in adults and children and there have been no serious health concerns reported. The study antibody is different from this "parent" because of 2 changes made to its structure. We think these changes will help block HIV from attaching to cells in your immune system, called CD4-T cells, that usually fight HIV if a person is ever exposed to it, and will make the study antibody last longer in the body. Otherwise the two antibodies are the same.

Lab-made antibodies given to a person usually do not last in the body more than a few months. One of the goals of this study is to see how long these study antibodies will stay in the body. We don't know yet how long they will last, but we think it may be several months.

Risks of the study antibodies:

VRC01.23LS:

Because the study antibody is being given to people for the first time in another ongoing study, we do not know what all of the risks may be. We think that the

risks will be similar to the risks seen with an earlier "parent" version of the study antibody called VRC01LS. In studies of the parent antibody some participants said that they felt mild pain and tenderness where they got the IV drip, but most participants described this as mild and could continue with their daily activities. The other side effects that were reported were the same as the general risks of antibodies described below, and people described them as mild to moderate. Overall, safety data from the other studies have found that VRC01LS is safe and does not cause serious health problems when given at the same doses that will be used in this study.

PGT121.414.LS and PDGM1400LS:

Both PGT121.414.LS and PDGM1400LS have been given alone to 9 people using an IV drip, and in combination with other study antibodies to 58 people using an IV drip, in 2 different studies. In the HVTN136/HPTN092 study which tested PGT121.414.LS and another antibody, 3 people had a headache, mild chills, muscle aches, nausea with vomiting and tiredness soon after the infusion but these went away after 15 minutes. One of these people had these side effects after 2 of 3 of their infusions, but they went away after fifteen minutes. They also had stiffness in their joints which went away after an hour.

In the HVTN140/HPTN101 study, PGT121.414.LS was given with PGDM1400LS and a third antibody. So far, no serious concerns have been seen. Similar to the previous studies, people had mild to moderate headaches, chills, sweating, nausea, fever, tiredness, pain, reddening and hardening of the skin at the infusion site, muscle pain and joint stiffness. One person had lightheadedness, muscle weakness, blurred vision, feeling faint, chills, muscle ache, ringing in the ears, and tiredness. However, all of these went away within 2 days.

This section lists the side effects we know about. There may be others that we don't yet know about, even serious ones. We will tell you if we learn about any new side effects. Based on what we have seen so far in ongoing studies, we think that the risks will be similar to the general risks described below.

General risks of antibodies:

Other kinds of antibodies used for other health problems have caused side effects within the first 24 hours of getting the antibody. Those antibodies have caused fever, chills, itchiness, rash, hives, redness in the cheeks and neck, lip or face swelling, nausea, vomiting, diarrhea, pain, headache, fatigue, dizziness, shaking, trouble breathing, high or low blood pressure, racing heartbeat, and chest pain. Some of these reactions have been seen in the studies using earlier versions of the study antibody, but they were mild and did not affect most participants' daily lives.

These reactions may be related to how an antibody is made, what it targets, or how fast the IV drip is given. Sometimes, the side effects include reactions at the place where the IV drip was given.

Joining the study

4. **It is completely up to you whether or not to join the study.**

   Take your time in deciding. If it helps, talk to people you trust, such as your doctor, friends, or family. If you decide not to join this study, or if you leave it after you have joined, your other care at this clinic and the benefits or rights you would normally have will not be affected.

   If you join this study, you may not be allowed to join some other HIV prevention studies now or in the future. You cannot be in this study while you are in another study where you get a study product. Being in more than 1 study may not be safe. We check to make sure that you are not in more than 1 study by taking your fingerprint on an electronic system. This information is only accessed by a few members of the study team using a secure password.

   You should not donate blood or tissue during the study.

   If you choose not to join this study, you may be able to join another study.

Site: Remove item 5 if you use a separate screening consent that covers these procedures.

5. **If you want to join the study, we will screen you to see if you are eligible.**

   Screening involves a physical exam, HIV test, and health history. A physical exam may include, but is not limited to:

   - Checking your weight, temperature, and blood pressure
   - Looking in your mouth and throat
   - Checking your veins to see how easy it might be to start an infusion
   - Looking at your skin
   - Listening to your heart and lungs
   - Feeling your abdomen (stomach and liver)
   - Asking you about vaccines you have gotten recently.

   We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are doing. We will ask you about medications you are taking. We will ask you about behaviors that might make you more likely to acquire HIV.

If you are capable of becoming pregnant, we will test you for pregnancy. If you have had your uterus or ovaries removed (a hysterectomy or oophorectomy), and this is verified by medical records, you are not required to have a pregnancy test.

We will review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

Site: adapt the following section so it is applicable to the care available at your site

6. **If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here for free.**

   For the care that we cannot give, we will explain how we will help you get care elsewhere. For health problems that are unrelated to the study, we will not pay for care.

7. **If you could become pregnant, you must agree to use contraception to join this study.**

Site: If you want to include Appendix C, Approved contraception methods (for sample informed consent form), in this consent form, paste it below and delete paragraph below.

You should not become pregnant during the study because we do not know how the study antibodies could affect the developing baby. You must agree to use effective contraception from 21 days before your first IV drip until 8 weeks after your last clinic visit. We will talk to you about effective contraception methods. They are listed on a handout that we will give to you.

You also should not begin the process to have your eggs collected from 21 days before your first IV drip until 8 weeks after your last clinic visit. If this is something you are considering, please discuss it with your study doctor and your fertility specialist.

Being in the study

If you meet the study requirements and want to join, here is what will happen:

8. **You will come to the clinic for scheduled visits about 10 times over 12 months.**

Site: Insert range of visit lengths, noting the different visit lengths for infusion visits and other follow-up visits.

Most of the visits will be 1-2 months apart. Each time you get the study antibodies, we will also ask you to come to the clinic for follow-up visits about 3 and 6 days after the IV drip to collect a blood sample. We will do this so that we

can look at how your body responds to the study products. Visits where you get an IV drip can last from [#] to [#] hours. Other visits will be from [#] to [#] hours.

You may have to come for more visits if you have a lab or health issue.

We may contact you after the study ends (for example, to tell you about the study results).

9. **We will give you [Site: Insert compensation] for each study visit you complete.**

   This amount is to cover the costs of [Site: Insert text]

Site: Insert any costs to participants (eg, contraception costs for participants who could become pregnant).

You do not have to pay anything to be in this study.

10. **We will give you the study antibodies using an IV drip.**

    For the IV drip, we will use a sterile needle to place a small plastic tube into a vein in your arm or hand. The small plastic tube is connected to a small bag of fluid that contains the study antibody. A pump controls how fast the fluid drips from the bag, through the tube, and into your vein. Each antibody will be given in a separate IV drip, one after the other. If you have any symptoms while you are getting the study antibodies, tell the study staff. Slowing or stopping the flow rate may help improve the symptom.

    At the first visit, the IV drip will take about 1 hour for each study antibody. The second IV drip visit will take about 15-30 minutes for each study antibody.

11. **We will give you the study antibodies on a schedule.**

    You will be in in either Group 4, 5, 6, 7 or 8 (Groups 1-3 were in Part A of the study). You will get IV drips at 2 visits during the study scheduled 6 months apart, as shown in the table below. The difference between the groups is the dose of each study antibody being given, but everyone will get all 3 study antibodies. You have an equal chance of being in Groups 4-7, and a higher chance of being in Group 8 because it is larger.

    The doses of the study antibodies will be adjusted for your body weight. We will weigh you to determine the correct amount before giving you the IV drip.

Study Groups and Infusion Schedule							
Group	Number of participants	Dose of each antibody			How it is given	Enrollment Visit	6 months later
		VRC01.23LS	PGT121.414.LS	PGDM1400LS			
4	8	Lower	Lower	Lower	IV drip	X	X
5	8	Medium	Lower	Lower	IV drip	X	X
6	8	Medium	Medium	Medium	IV drip	X	X
7	8	Higher	Lower	Lower	IV drip	X	X
8	30	Higher	Higher	Higher	IV drip	X	X

You will have to wait in the clinic for about 1 hour after getting the IV drip to see if there are any problems. We will collect a blood sample about 1 hour after thedrip is finished. Then, for that night and for 3 more days, you will need to keep track in a diary about how you are feeling and if you have any symptoms. *Site: Customize the next sentence based on how you collect reactogenicity information.* We will review the diary with you during the 2 visits after you get the IV drips. You will turn in the diary by the day 6 visit after the first IV drip. We will contact you about 4 days after the second IV drip to collect the information from your diary. Contact the clinic staff if you have any issues or concerns after getting anIV drip. If you have a problem, we will continue to check on you until it goes away.

12. In addition to giving you the study antibodies, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid HIV
- Do physical exams
- Do pregnancy tests if you could become pregnant
- Ask questions about your health, including medications you may be taking, including pre-exposure prophylaxis (PrEP)
- Ask questions about any personal problems or benefits you may have from being in the study
- Ask questions about yor experience getting the IV drip
- Take urine and blood samples

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 25 mL and 97 mL (a little less than 2 tablespoons to a little less than ½ cup). Your body will make new blood to replace the blood we take out.

Site: You may want to add a sentence to the end of the previous paragraph contextualizing the blood volumes described (eg, "To compare, people who

donate blood in the US can give a total of about 500 mL in an 8-week period.”). Modify the example for cultural relevance and alter blood volumes as necessary.

Site: Insert Appendix E, Table of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.

We will be looking for side effects. We will review the results of these procedures and tests with you at your next visit, or sooner if necessary. If any of the results are important to your health, we will tell you.

13. Getting approved vaccines while you are in this study is allowed.

If you are planning to get any approved vaccines, please tell us so that we can schedule your study visits with this in mind. To be sure that we can answer the study questions, we will not give the study infusion within 7 days before or after you get a COVID-19 vaccine. We will wait 2-4 weeks before or after you get a vaccine for MPOX.

14. We will counsel you about protecting yourself from HIV.

We will ask you personal questions about factors that may make you more likely to acquire HIV, such as sexual behavior, alcohol, and drug use. We will talk with you about ways to keep your likelihood of acquiring HIV low.

15. We will test your samples.

We will send your samples (without your name) to labs approved by the HVTN and HPTN for this study, which are located in the United States and South Africa. In rare cases, some of your samples may be sent to labs approved by the HVTN and HPTN in other countries for research related to this study.

Researchers will look at how your body, including your immune system, responds to the study vaccine. They may also look at how your body responds to infections and other vaccines. They may use your samples to improve or create new lab tests.

Researchers may also do genetic testing related to this study on your samples. Your genes are passed to you from your birth parents. They affect how you look and how your body works. The genetic testing will only involve some of your genes, not all of your genes (your genome). It will involve genes related to the immune system and HIV.

If you get HIV, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and how the virus is impacted by the study vaccine.

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

These tests done on your samples are for research purposes, not to check your health. The labs will not give the results to you or this clinic because their tests are not approved for use in making health care decisions. These labs are only approved to do research tests.

When your samples are no longer needed for this study, the HVTN and HPTN will continue to store them.

16. We will do our best to protect your private information.

Your study records and samples will be kept in a secure location. We will label all of your samples and most of your records with a code number, not your name or other personal information. However, it is possible to identify you, if necessary. We will not share your name with the lab that does the tests on your samples, or with anyone else who does not need to know your name.

Clinic staff will have access to your study records. Your records may also be reviewed by groups who watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health (NIH)/Division of AIDS (DAIDS), and its study monitors,
- Any regulatory agency that reviews clinical trials,
- [Insert name of local IRB/EC] ,
- South African Health Products Regulatory Authority (SAHPRA)
- [Insert name of local and/or national regulatory authority as appropriate],
- The HVTN, HPTN, and the people who work for them,
- The Safety Monitoring Board and
- The US Office for Human Research Protections (OHRP).

All reviewers will take steps to keep your records private.

We cannot guarantee absolute privacy. If you are found to have a medical condition that we are required to report by law, then some of your information may be shared. At this clinic, we have to report the following information:

Site: Include any public health or legal reporting requirements, including SARS-CoV-2/COVID-19. Bulleted examples should include all appropriate cases (reportable

communicable disease, risk of harm to self or others, etc.). If your site does not have public health or legal reporting requirements, you may delete the last sentence in the paragraph above, along with the bullets below.

- [Item 1]
- [Item 2]
- [Item 3]

In addition, the Protection of Personal Information Act (POPIA) ensures that all South African institutions conduct themselves in a responsible manner when collecting, processing, storing, and sharing another entity's personal information by holding them accountable should they abuse or compromise your personal information in any way.

The results of this study may be published. No publication will use your name or identify you personally.

We may share information from the study with other researchers. We will not share your name or information that can identify you.

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

Leaving the study

17. We may stop your infusions even if you want to stay in the study and even if you were scheduled for more infusions.

If you become pregnant, we will encourage you to stay in the study, but it will be your choice. You may complete study procedures unless there is a medical reason not to. If you leave the study while you are still pregnant, we will contact you after your due date to ask some questions about your pregnancy and delivery if you agree.

If you acquire HIV, we will also take fewer samples, and we will help you get care and support. We will encourage you to stay in the study if you choose. We will counsel you about having HIV and about telling your partner(s). *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

18. We may take you out of the study at any time.

We may take you out of the study if:

- You do not follow instructions,
- We think that staying in the study might harm you,
- The study is stopped for any reason.

19. Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

Previously collected information about you will remain in the study records and will be included in the analysis of results. Your information can not be removed from the study records.

We may ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We may also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Other Risks

20. There are other risks to being in this study.

This section describes the other risks and restrictions we know about. There may also be unknown risks, even serious ones. We will tell you if we learn anything new that may affect your willingness to stay in the study.

Risks of abnormal laboratory results

Minor changes in test results occasionally happen. This means that the test results can be abnormal even if you have no illness or problem. If this happens, we may ask you to come back to the clinic to be retested. This may cause you to worry, and it may be inconvenient to come back to the clinic. If we determine you have a health problem, we will provide care or help you get the care you need.

Risks of giving blood:

Giving blood can cause bruising, pain, fainting, soreness, redness, swelling, itching, bleeding, and infection (rarely). Giving blood can cause a low blood-cell count (anemia), making you feel tired.

Risks of getting an IV drip:

Getting an IV may cause stinging, discomfort, pain, soreness, redness, bruising, itching, rash, and swelling where the needle goes into the skin. Rarely, needle sticks can result in a blood clot or infection.

Personal problems/discrimination:

Some people who join HVTN and HPTN studies report personal problems or discrimination because of joining an HIV prevention study. Family or friends may worry, get upset or angry, or assume that you have HIV or are likely to acquire HIV and treat you unfairly as a result. Rarely, a person has lost a job because the study took too much time away from work, or because their employer thought they had HIV.

HIV testing:

HIV antibody tests are the usual way to test for HIV. We are still learning how HIV tests perform when people are given study antibodies. We have used several common HIV antibody tests to test samples of blood containing antibodies similar to the study antibodies. We found that very high levels of these similar antibodies can cause positive or uncertain results on some HIV tests. You may have such high levels for a short time after you get the study antibodies. This means that for a few days after getting the study antibodies, some HIV tests might say you have HIV, even if you don't.

For this reason, you should plan to get HIV tests only at this clinic during the study. Our tests can truly detect HIV. They can also tell if someone does not have HIV. We do not expect you to have any problems with HIV testing after the study ends.

Embarrassment/anxiety:

You may feel embarrassed when we ask questions about behaviors that may make you more likely to acquire HIV, such as having sex and using drugs. Also, waiting for your HIV test results or other health test results could make you feel anxious. You could feel worried if your test results show that you have HIV. If you feel embarrassed or anxious, please tell us and we will try to help you.

Risks of disclosure of your personal information:

We will take several steps to protect your personal information. Although the risk is very low, it is possible that your personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like.

Risks of genetic testing:

It is unlikely, but the genetic tests done on your samples could show that you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

Unknown risks:

We do not know if the study antibodies will increase, decrease, or not change your likelihood of getting HIV if you are exposed. If you get HIV, we do not know how the study antibodies might affect HIV or how long it takes to develop AIDS.

We do not know if getting these study antibodies will affect how you respond to any future approved HIV antibody or vaccine. Currently, no HIV antibody or vaccine has been approved for use.

We do not know how the study antibodies will affect a pregnant participant or a developing baby.

Benefits

21. The study may not benefit you.

We do not expect the study antibodies to benefit you in any way. However, being in the study might still help you in some ways. The counseling that you get as part of the study may help you avoid getting HIV. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about.

When asked, some HIV vaccine study participants said that participating in a study made them feel good about helping others and increased their knowledge about HIV.

This study may help in the search for an antibody or vaccine to prevent HIV. However, if the study antibodies or a vaccine later become approved and sold, there are no plans to share any money with you.

Your rights and responsibilities

22. If you join the study, you have rights and responsibilities.

You have many rights that we will respect. You also have responsibilities. We list these in the Bill of Rights and Responsibilities for Research. We will give you a copy of it.

Injuries

Sites: Approval from HVTN Regulatory Affairs (at vtn.core.reg@hvtn.org) is needed for any change (other than those that the instructions specifically request or those previously approved by HVTN Regulatory Affairs) to the boxed text. You can remove the box around the text.

23. If you get sick or injured during the study, contact us immediately.

Your health is important to us. *(Sites: adjust the following 2 sentences if applicable to the care available at your site)* We will tell you about the care that we can give here. For the care that we cannot provide, we will explain how we will help you get care elsewhere.

If you become sick or injured in this study, the HVTN has a process to decide if it is related to the study products and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries.

In this study, our clinic has insurance to cover your medical treatment in the case of a study-related injury. We will follow the Association of the British Pharmaceutical Industry guidelines for payment of study-related injury. We can give you a copy of these guidelines. In rare cases, the insurance funds may not be enough.

The HVTN has limited funds to pay medical costs that it determines are reasonable.If the injury is not study related, then you and/or your health insurance will be responsible for treatment costs.

Some injuries are not physical. For example, you might be harmed emotionally by being in an HIV prevention study. Or you might lose wages because you cannot go to work. However, there are no funds to pay for these kinds of injuries, even if they are study related.

You may disagree with the decision about whether your injury is study related. If you wish, the HVTN will ask independent experts to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

24. If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact
[name or title and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact
[name or title and telephone number of the investigator or other study staff].

This study has been reviewed and approved by a committee called the [name of local IRB/EC]. If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name or title and telephone number of person on IRB/EC] at the committee.

The study has been structured in accordance with the Declaration of Helsinki (last updated October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants, *the Ethics in Health Research: Principles, Structures and Processes Second Edition 2015, and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.* We can provide you with copies of these guidelines if you wish to review them.

If you want to leave this study, contact
[name or title and telephone number of the investigator or other study staff].

You can reach a study staff member 24 hours a day at [telephone number].

If you have questions about this trial, you should first discuss them with your doctor or the Ethics Committee (contact details as provided on this form). After you have consulted your doctor or the Ethics Committee, and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park
Building A
402 Kirkness Street
Arcadia, Pretoria
0083
E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

Your permissions and signature

25. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.

- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)	Participant's signature or mark	Date	Time

Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the entire discussion of this consent form.

Appendix C Approved contraception methods (for sample informed consent form)

Site: Any change to the following boxed text requires approval from HVTN Regulatory Affairs at vtn.core.reg@hvtn.org. You can remove the box around the text.

You should not become pregnant during the study because we do not know how the study antibodies could affect the developing baby.

You must agree to use effective contraception from 21 days before your first IV drip until 8 weeks after your last scheduled clinic visit.

Effective contraception means using one of the following methods:

- Contraceptive drugs that prevent pregnancy, used consistently as prescribed (given by pills, shots, patches, vaginal rings, or inserts under the skin);
- Internal or external condoms every time you have sex, with or without a cream or gel that kills sperm;
- Diaphragm or cervical cap every time you have sex with a cream or gel that kills sperm;
- Intrauterine device (IUD); or
- Any other contraceptive method approved by the researchers.

You do not have to use contraception if:

- You are only having sex with a partner or partners who have had a vasectomy. (We will ask you some questions to confirm that the vasectomy was successful.);
- You have reached menopause, with no menstrual periods for 1 year;
- You have had a hysterectomy (your uterus removed);
- You have had your ovaries removed;
- You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes;
- You are having sex only with a partner(s) assigned female sex at birth (AFAB);
- You only have oral sex and/or anal sex;

- You do not have sexual partners assigned male sex at birth (AMAB); or,
- You are sexually abstinent (no sex at all).

Remember: If you are having sex, internal and external condoms are the only contraception methods that also provide protection against HIV and other sexually transmitted infections (STIs).

If you join the study, we will test you for pregnancy at some visits, including before each IV drip.

Appendix D Sample consent form for use of samples and information in other studies

Title: A phase 1 clinical trial to evaluate the safety, tolerability, and pharmacokinetics of monoclonal antibodies VRC01.23LS, PGT121.414.LS and PGDM1400LS administered via intravenous infusion in adults without HIV

Protocol number: HVTN 143/HPTN 109

Site: [Insert site name]

When samples are no longer needed for this study, the HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN) want to use them in other studies and share them with other researchers. The HVTN and HTPN call these samples called "extra samples." The HVTN and HPTN will only allow your extra samples to be used in other studies if you agree to this. You will mark your decision at the end of this form. If you have any questions, please ask.

1. Do I have to agree?

No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

2. Where are the samples stored?

Extra samples are stored in a secure, central place called a repository. Your samples will be stored in the HVTN repository in South Africa.

3. How long will the samples be stored?

There is no limit on how long your extra samples will be stored. *[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]*

4. Will I be paid for the use of my samples?

No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

5. Will I benefit from allowing my samples to be used in other studies?

Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not part of your medical record. The studies are only being done for research purposes.

6. Will the HVTN or HPTN sell my samples and information?

No, but the HVTN and HPTN may share your samples with HVTN, HPTN, or other researchers. Once we share your samples and information, we may not be able to get them back.

7. How do other researchers get my samples and information?

When a researcher wants to use your samples and information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's Institutional Review Board (IRB) or Ethics Committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN will send your samples to the researcher's location.

8. What information is shared with HVTN, HPTN, or other researchers?

The samples and information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study antibodies you received and how your body responded to the study antibodies.

9. What kind of studies might be done with my extra samples and information?

The studies will be related to HIV, vaccines, antibodies, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

If you agree, your samples could also be used for genome-wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it, but your name and other personal information will not be included. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small. There may be other unknown risks.

10. What are the risks of genetic testing?

It is unlikely, but the genetic tests done on your samples could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your

test results from the genetic testing. The results are not part of your study records and are not given to you.

11. Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your extra samples and information for other research
- Government agencies that fund or monitor the research using your extra samples and information
- Any regulatory agency that reviews clinical trials
- The researcher's IRB or EC
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples and information may be published. No publication will use your name or identify you personally.

Questions

12. If you have questions or problems about allowing your samples and information to be used in other studies, use the following important contacts.

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact
[name or title and telephone number of the investigator or other study staff].

If you think you may have been harmed because of studies using your samples or information, contact
[name or title and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, contact
[name or title and telephone number of person on IRB/EC .

The study has been structured in accordance with the Declaration of Helsinki (last updated October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants, *the Ethics in Health Research: Principles, Structures and Processes Second Edition 2015, and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa*. We can provide you with copies of these guidelines if you wish to review them.

You can reach a study staff member 24 hours a day at [telephone number].

If you have questions about this trial, you should first discuss them with your doctor or the EC (contact details as provided on this form). After you have consulted your doctor or the EC, and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park
Building A
402 Kirkness Street
Arcadia, Pretoria
0083
E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

13. **Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your choice about how your samples and information can be used. You can change your mind after signing this form.**

☐ I allow my extra samples and information to be used for other studies related to HIV, vaccines, antibodies, the immune system, and other diseases. This may include genetic testing.

OR

☐ I agree to the option above *and* also to allow my extra samples and information to be used in genome-wide studies.

OR

☐ I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing or genome-wide studies.

Participant's name (print)	Participant's signature or mark	Date	Time

Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the entire discussion of this consent form.

Appendix E Table of procedures (for sample informed consent form)

Part A			**Time after the enrollment visit**					
Procedure	**Screening visit(s)**	**Enrollment Visit**	**3 days**	**6 days**	**1 month**	**2 months**	**4 months**	**6 months**
IV drip		√						
Medical history	√							
Complete physical	√							√
Brief physical		√	√	√	√	√	√	
Urine test	√					√		√
Blood drawn	√	√	√	√	√	√	√	√
Pregnancy test (participants capable of becoming pregnant)*	√	√						√
HIV testing and counseling	√						√	√
Risk-reduction counseling	√	√			√	√	√	√
Interview/questionnaire	√	√	√	√	√	√	√	√

* People who had a hysterectomy (removal of the uterus) or removal of both ovaries (verified by medical records) are not required to have a pregnancy test.

Part B			Time after the enrollment visit									
Procedure	**Screening visit(s)**	**Enrollment visit**	**3 days**	**6 days**	**1 month**	**2 months**	**4 months**	**6 months**	**6 months + 4 days (phone contact only)**	**8 months**	**10 months**	**12 months**
IV/drip		√						√				
Medical history	√											
Complete physical	√											√
Brief physical		√	√	√	√	√	√	√		√	√	
Urine test	√					√						√
Blood drawn	√	√	√	√	√	√	√	√		√	√	√
Pregnancy test (participants of pregnancy potential)*	√	√						√				√
HIV testing and pretest counseling	√						√			√		√
Risk-reduction counseling	√	√			√	√	√	√		√	√	√
Interview/questionnaire	√	√	√	√	√	√	√	√	√	√	√	√

* Persons who had a hysterectomy (removal of the uterus) or removal of both ovaries (verified by medical records) are not required to have a pregnancy test.

Appendix F Laboratory procedures for Part A

					Visit:	1	2	3	4	5	6	7	8
					Day:	Screening visit[3]	D1	D4	D7	D29	D57	D113	D169
					Week:		W0			W4	W8	W16	W24
							Study Product Administration						
Procedure	**Ship to[1]**	**Assay location[2]**	**Tube Type[4]**	**Tube size (vol. capacity)[4]**			**VRC01.23LS**						
BLOOD COLLECTION													
Screening/Diagnostic													
Screening HIV test	Local lab	Local lab	EDTA	5mL		5	—	—	—	—	—	—	—
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—
Syphilis[9]	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—
HIV diagnostics[7]	HSML-NICD	HSML-NICD	EDTA	10mL		—	—	—	—	—	—	—	10
Safety labs[10]													
CBC/ Differential	Local lab	Local lab	EDTA	5mL		5	5	—	—	—	5	—	5
Chemistry Panel[5]	Local lab	Local lab	SST	5mL		5	5	—	—	—	5	—	5
Drug concentrations/detection													
VRC01.23LS concentration	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	y
1 hour Post Study Product Administration VRC01.23LS concentration[14]	CSR	HVTN Labs	SST	8.5mL		—	8.5	—	—	—	—	—	—
Humoral assays													
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	y
Non-neutralizing antiviral assays[16]	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	y
Anti-Drug Antibody (ADA)													
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	—	y
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	—	y
Ab Reaction[11]													
Tryptase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL		—	See footnote 12						
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	—	—
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	—	—
STORAGE													
Serum	CSR	—	SST	8.5mL		—	68.0	42.5	42.5	42.5	42.5	42.5	42.5
Visit total						**25**	**86.5**	**42.5**	**42.5**	**42.5**	**52.5**	**42.5**	**62.5**
56-Day total[13]						**25**	**112**	**154**	**197**	**239**	**292**	**95**	**105**
URINE COLLECTION[10]													
Urine dipstick[8]	Local lab	Local lab				X	—	—	—	—	X	—	X
Pregnancy test[6]	Local lab	Local lab				X	X[15]	—	—	—	—	—	X

Footnotes for Appendix F:

[1] CSR = central specimen repository, HSML-NICD = HIV Seromolecular Laboratory – National Institute for Communicable Diseases (Johannesburg, South Africa)

[2] HVTN laboratories include: Duke University Medical Center (Durham, North Carolina, USA); South African Immunology Laboratory-National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Dartmouth College (Hanover, New Hampshire, USA).
Non-HVTN laboratories include: ARUP Laboratories (Salt Lake City, Utah, USA).

[3] Screening may occur over the course of several contacts/visits, up to and including day 1 prior to study-product administration.

[4] Local labs may assign appropriate alternative specimen type or tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment) and Sections 9.3 and 9.4 (enrollment and follow-up).

[6] For participants who are of pregnancy potential, pregnancy test must be performed on urine or blood specimens on the day of study-product administration with negative results received prior to administration. Persons who are NOT of pregnancy potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing.

[7] At an early-termination visit for a withdrawn or terminated participant who does not have HIV (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 8 above. If a participant has a confirmed diagnosis of HIV, do not collect blood for HIV diagnostic testing (see Section 9.12).

[8] Urine testing is described in Section 9.7 and microscopy if needed.

[9] Syphilis testing will be done by serology.

[10] For participants with confirmed diagnosis of HIV, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests will be collected.

[11] To investigate antibody (Ab)-administration–related clinical reactions, assays may be performed on serum samples taken prior to the study-product administration associated with the reaction and collected after the onset of reaction. Refer to the study-specific procedures (SSP) for more information.

[12] Serum-separating tube (SST) blood will be collected at specific timepoints after the onset of any Ab reaction. Refer to the SSP for more information.

[13] The 56-day total blood volume does not include up to 34 mL SST blood collected for any Ab reaction; however, the 56-day limit is not exceeded at any visit by the possible collection of SST blood for an Ab reaction.

[14] 8.5 mL of SST blood will be **collected post–study-product administration** (see SSP for details).

[15] Pregnancy test at enrollment does not need to be performed if negative results are received from screening pregnancy test conducted within 48 hours prior to study-product administration.

y = SST blood collected for serum storage will also cover specimen needs for drug concentrations, HIV-1 neutralizing Ab assays, non-neutralizing antiviral assays, and antidrug antibody (ADA) detection and functional assays (including for any Ab reactions); no separate blood draw is needed. The SST blood for Serum storage is collected prior to study product administration.

Appendix G Laboratory procedures for Part B

					Visit:	1	2	3	4	5	6	7	8	9	10	11	12
					Day:	Screening visit[3]	D1	D4	D7	D29	D57	D113	D169	D173[16]	D225	D304	D365
					Week:		W0			W4	W8	W16	W24		W32	W40	W48
							Study Product Administration #1						**Study Product Administration #2**				
Procedure	**Ship to[1]**	**Assay location[2]**	**Tube Type[4]**	**Tube size (vol. capacity)[4]**			**VRC01.23LS + PGT121.414.LS + PGDM1400LS**						**VRC01.23LS + PGT121.414.LS + PGDM1400LS**				
BLOOD COLLECTION																	
Screening/Diagnostic																	
Screening HIV test	Local lab	Local lab	EDTA	5mL		5	—	—	—	—	—	—	—	—	—	—	—
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—	—
Syphilis[9]	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—	—
HIV diagnostics[7]	HSML-NICD	HSML-NICD	EDTA	10mL		—	—	—	—	—	—	10	—	—	10	—	10
Safety labs[10]																	
CBC/ Differential	Local lab	Local lab	EDTA	5mL		5	5	—	—	—	5	—	5	—	5	—	5
Chemistry Panel[5]	Local lab	Local lab	SST	5mL		5	5	—	—	—	5	—	5	—	5	—	5
Drug concentrations/detection																	
VRC01.23LS, PGT121.414.LS and PGDM1400LS concentration	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	y	—	y	y	y
1 hour Post Study Product Administration VRC01.23LS, PGT121.414.LS and PGDM1400LS concentration[14]	CSR	HVTN Labs	SST	8.5mL		—	8.5	—	—	—	—	—	8.5	—	—	—	—
Humoral assays																	
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	y	—	y	y	y
Non-neutralizing antiviral assays[17]	CSR	HVTN Labs	SST	8.5mL		—	y	y	y	y	y	y	y	—	y	y	y
Anti-Drug Antibody (ADA)																	
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	y	—	—	—	y	y
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	y	—	—	—	y	y
Ab Reaction[11]																	
Tryptase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL		—	See footnote 12										
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	—	See footnote y	—	—	—	—
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	—	See footnote y	—	—	—	—
STORAGE																	
Serum	CSR	—	SST	8.5mL		—	68.0	42.5	42.5	42.5	42.5	42.5	42.5	–	42.5	42.5	42.5
Visit total						**25**	**86.5**	**42.5**	**42.5**	**42.5**	**52.5**	**53**	**61.0**	**0**	**62.5**	**42.5**	**62.5**
56-Day total[13]						**25**	**112**	**154**	**197**	**239**	**292**	**53**	**114**	**61**	**124**	**105**	**168**
URINE COLLECTION[10]																	
Urine dipstick[8]	Local lab	Local lab				X	—	—	—	—	X	—	—	—	—	—	X
Pregnancy test[6]	Local lab	Local lab				X	X[15]	—	—	—	—	—	X	—	—	—	X

Footnotes for Appendix G:

[1] CSR = central specimen repository; HSML-NICD = HIV Seromolecular Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa)

[2] HVTN laboratories include: Duke University Medical Center (Durham, North Carolina, USA); South African Immunology Laboratory-National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Dartmouth College (Hanover, New Hampshire, USA).
Non-HVTN laboratories include: ARUP Laboratories (Salt Lake City, Utah, USA)

[3] Screening may occur over the course of several contacts/visits, up to and including day 1 prior to study-product administration.

[4] Local labs may assign appropriate alternative specimen type or tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment), and Sections 9.3 and 9.4 (enrollment and follow-up).

[6] For participants who are of pregnancy potential, pregnancy test must be performed on urine or blood specimens on the day of study-product administration with negative results received prior to administration. Persons who are NOT of pregnancy potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing.

[7] At an early-termination visit for a withdrawn or terminated participant who does not have HIV (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 12 above. If a participant has a confirmed diagnosis of HIV, do not collect blood for HIV diagnostic testing (see Section 9.12).

[8] Urine testing is described in Section 9.7 andmicroscopy if needed.

[9] Syphilis testing will be done by serology.

[10] For participants with confirmed diagnosis of HIV, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests will be collected.

[11] To investigate antibody (Ab)-administration–related clinical reactions, assays may be performed on serum samples taken prior to the study-product administration associated with the reaction and collected after the onset of reaction. Refer to the study-specific procedures (SSP) for more information.

[12] Serum-separating tube (SST) blood will be collected at specific timepoints after the onset of any Ab reaction. Refer to the SSP for more information.

[13] The 56-day total blood volume does not include up to 51 mL SST blood collected for any Ab reaction; however, the 56-day limit is not exceeded at any visit by the possible collection of SST blood for an Ab reaction.

[14] 8.5 mL of SST blood will be collected post–study-product administration (see SSP for details).

[15] Pregnancy test at enrollment does not need to be performed if negative results from screening pregnancy test are received prior to study-product administration on the day of study-product administration.

[16] Phone contact only. No specimen collection at this visit.

y = SST blood collected for serum storage will also cover specimen needs for drug concentrations, HIV-1 neutralizing Ab assays, non-neutralizing antiviral assays, and antidrug antibody (ADA) detection and functional assays (including for any Ab reactions); no separate blood draw is needed. The SST blood for Serum storage is collected prior to study product administration.

Appendix H Procedures at CRS for Part A

Visit	01[1]	02[2]	03	04	05	06	07	08	Post
Day		D1	D4	D7	D29	D57	D113	D169	
Week		W0	W0	W0	W4	W8	W16	W24	
Procedure	Scr	Inf							
Study procedures									
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—
Assessment of Understanding (AoU)	X	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	X	—
Confirm eligibility, obtain demographics	X	—	—	—	—	—	—	—	—
Infusion	—	X	—	—	—	—	—	—	—
Solicited AE assessment[3]	—	X[3]	X[3]	X[3]	—	—	—	—	—
Abbreviated physical exam	—	X	X	X	X	X	X	—	—
Risk-reduction counseling[4]	X	X	—	—	X	X	X	X	—
Contraception status assessment[5]	X	X	—	—	X	X	X	X	—
Social impact assessment	—	X	—	—	X	X	X	X	—
Behavioral assessment questionnaire[6]	X	—	—	—	—	—	—	X	—
Social impact assessment questionnaire	—	—	—	—	—	X	—	X	—
Acceptability questionnaire	—	X	—	—	—	—	—	—	—
Outside testing and belief questionnaire	—	—	—	—	—	—	—	X	
Concomitant medications	X	X	X	X	X	X	X	X	—
Intercurrent illness/unsolicited AE assessment	—	X	X	X	X	X	X	X	—
HIV assessment[7]	X	—	—	—	—	—	X	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	X	X
Specimen collection [8]	X	X	X	X	X	X	X	X	—

Footnotes for Appendix H:

[1] Screening may occur over the course of several contacts/visits, up to and including day 1 prior to study-product administration.

[2] Specimens collected at day 1 may be obtained within the 14 days prior to study-product administration, except for a pregnancy test, which must be performed on urine or blood specimens within 48 hours prior to study-product administration with negative results received prior to study-product administration.

[3] Solicited adverse event (AE) assessments are performed daily for at least 3 full days following study-product administration. Clinical research site (CRS) staff will review and reconcile the diary with the participant and then report solicited AEs. Participant diary reconciliation may happen as the data is available (see the HVTN 143/HPTN 109 study-specific procedures [SSP]).

[4] Includes transmission risk-reduction counseling for participants living with HIV.

[5] Contraception status assessment is required only for participants who are of pregnancy potential.

[6] Not applicable to participants living with HIV.

[7] Includes pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant. Not applicable for participants diagnosed with HIV.

[8] For specimen collection requirements, see Appendix F.

Appendix I Procedures at CRS for Part B

Visit	01[1]	02[2]	03	04	05	06	07	08	09	10	11	12	Post
Day		D1	D4	D7	D29	D57	D113	D169	D173	D225	D304	D365	
Week		W0	W0	W0	W4	W8	W16	W24	W24	W32	W40	W48	
Procedure	Scr	Inf 1						Inf 2	Phone contact				
Study procedures													
Signed screening consent (if used)	X	—	—	—	—	—		—		—	—	—	—
Assessment of Understanding (AoU)	X	—	—	—	—	—		—		—	—	—	—
Signed protocol consent	X	—	—	—	—	—		—		—	—	—	—
Medical history	X	—	—	—	—	—		—		—	—	—	—
Complete physical exam	X	—	—	—	—	—		—		—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—		—		—	—	—	—
Infusion	—	X	—	—	—	—		X		—	—	—	—
Solicited AE assessment[3]	—	X[3]	X[3]	X[3]	—	—		X[3]	X[3]	—	—	—	—
Abbreviated physical exam	—	X	X	X	X	X	X	X		X	X	—	—
Risk-reduction counseling[4]	X	X	—	—	X	X	X	X		X	X	X	—
Contraception status assessment[5]	X	X	—	—	X	X	X	X		X	X	X	—
Social impact assessment	—	X	—	—	X	X	X	X		X	X	X	—
Behavioral assessment questionnaire[6]	X	—	—	—	—	—		—		—	—	X	—
Social impact assessment questionnaire	—	—	—	—	—	X		—		—	—	X	—
Acceptability questionnaire	—	X	—	—	—	—		X		—	—	—	—
Outside testing and belief questionnaire	—	—	—	—	—	—		—		—	—	X	
Concomitant medications	X	X	X	X	X	X	X	X		X	X	X	—
Intercurrent illness/unsolicited AE assessment	—	X	X	X	X	X	X	X		X	X	X	—
HIV assessment[7]	X	—	—	—	—	—	X			X	—	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—		—		—	—	X	X
Specimen collection [8]	X	X	X	X	X	X	X	X		X	X	X	—

Footnotes for Appendix I:

[1] Screening may occur over the course of several contacts/visits, up to and including day 1 prior to study-product administration.

[2] Specimens collected at day 1 may be obtained within the 14 days prior to study-product administration, except for a pregnancy test, which must be performed on urine or blood specimens within 48 hours prior to study-product administration with negative results received prior to study-product administration.

[3] Solicited adverse event (AE) assessments are performed daily for at least 3 full days following study-product administration. CRS staff will review and reconcile the diary with the participant and then report solicited AEs. Participant diary reconciliation may happen as the data is available (see the HVTN 143/HPTN 109 study-specific procedures [SSP]). For Part B participants' second infusion solicited AE data collection: remote documentation of the participant diary may occur after the solicited AE assessment period and the next clinic visit (visit 9) (see the HVTN 143/HPTN 109 SSP).

[4] Includes transmission risk-reduction counseling for participants living with HIV.

[5] Contraception status assessment is required only for participants who are of pregnancy potential.

[6] Not applicable to participants living with HIV.

[7] Includes pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant. Not applicable for participants diagnosed with HIV.

[8] For specimen collection requirements, see Appendix G.

Appendix J South African Guidelines for determining low likelihood of acquiring HIV

The following are intended as guidelines for the investigator to help identify potential trial participants with allow likelihood of acquiring HIV. These guidelines are based on behaviors within the last 12 months prior to enrollment; however, it may be appropriate to consider a volunteer's behavior over a longer period of time to effectively assess the volunteer's likelihood of acquiring HIV. Some volunteers may not be appropriate for enrollment even if they meet these guidelines. These guidelines should be supplemented and interpreted with local epidemiological information about HIV prevalence in your area and community networks. The investigator may review with the site Principal Investigator (PI) and/or the Protocol Safety Review Team (PSRT) a volunteer's likelihood of acquiring HIV.

Consider whether a volunteer would be appropriate for inclusion if, in the 12 months prior to enrollment, the person:

- Abstained from penile-vaginal and penile-anal intercourse, OR
- Was in a mutually monogamous relationship with a partner known to be living without HIV status, OR
- Had 1 partner known or believed to be living without HIV, with whom they regularly used condoms for penile-vaginal or penile-anal intercourse.

Exclude a volunteer if:

Within the 12 months prior to enrollment, a history of newly acquired syphilis; gonorrhea; chlamydia; trichomoniasis; active herpes simplex virus type 2 (HSV) lesions; chancroid; genital warts of the labia minora, vagina, or cervix; or any other symptomatic genital warts.

Appendix K Visit windows

Part A

Visit number	Visit type	Lower allowable window	Lower target day	Target day	Upper target day	Upper allowable window
1	Screening	-56	-		-	-
2	**Enrollment[1] Infusion**	-	-	1	-	-
3	3 days post infusion	-1	-	4	-	+1
4	6 days post infusion	-1	-	7	-	+2
5	4 weeks post infusion	-7	-3	29	+3	+7
6	8 weeks post infusion	-7	-3	57	+3	+7
7	16 weeks post infusion	-7	-3	113	+3	+7
8	24 weeks post infusion	-7	-3	169	+3	+7

Part B

Visit number	Visit type	Lower allowable window	Lower target day	Target day	Upper target day	Upper allowable window
1	Screening	-56	-		-	-
2	**Enrollment Infusion #1**	-	-	1	-	-
3	3 days post infusion #1	-1	-	4	-	+1
4	6 days post infusion #1	-1	-	7	-	+2
5	4 weeks post infusion #1	-7	-3	29	+3	+7
6	8 weeks post infusion #1	-7	-3	57	+3	+7
7	16 weeks post infusion #1	-7	-3	113	+3	+7
8	**Infusion #2**	-14	-7	169	+7	+14
9	4 days post infusion #2	-	-	173	+7	-
10	32 weeks post infusion #2	-7	-3	225	+3	+7
11	40 weeks post infusion #2	-7	-3	304	+3	+7
12	48 weeks post infusion #2	-7	-3	365	+3	+7

Appendix L Protocol Signature Page

A phase 1 clinical trial to evaluate the safety, tolerability, and pharmacokinetics of monoclonal antibodies VRC01.23LS, PGT121.414.LS and PGDM1400LS administered via intravenous infusion in adults without HIV

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice E6(R2); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (eg, US National Institutes of Health, Division of AIDS) and institutional policies

Investigator of Record Name (print)	Investigator of Record Signature	Date

DAIDS Protocol Number: HVTN 143/HPTN 109

DAIDS Protocol Version: Version 1.0

Protocol Date: June 07, 2023