HIV VACCINE TRIALS NETWORK

HPTN HIV Prevention Trials Network

PROTOCOL

HVTN 136/HPTN 092

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

DAIDS DOCUMENT ID 38634

IND TBD HELD BY DAIDS

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 PRODUCTS PROVIDED BY

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 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

Primary objectives

Primary objective 1

To evaluate the safety and tolerability of the PGT121.414.LS monoclonal antibody (mAb) when administered alone via intravenous (IV) or subcutaneous (SC) infusion (Part A) and of PGT121.414.LS and VRC07-523LS administered consecutively via IV or SC routes at and after each product administration visit (Part B).

Primary objective 2

To evaluate the serum concentrations and pharmacokinetic (PK) properties of PGT121.414.LS after a single administration (Part A) and of PGT121.414.LS and VRC07-523LS after consecutive administration of the pair of mAbs at and after each of 3 quarterly visits (Part B).

Primary objective 3

To evaluate the individual mAb-specific serum neutralizing activity of PGT121.414.LS after a single administration (Part A) and of PGT121.414.LS and VRC07-523LS after consecutive administration of the pair of mAbs at and after each of 3 quarterly visits (Part B).

Study products

- PGT121.BIJ414.LS (referenced and labeled as 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 the Collaboration for AIDS Vaccine Discovery (CAVD) investigators. The drug substance was manufactured under current Good Manufacturing Practice (cGMP) standards at Just Biotherapeutics under contract to DAIDS's Vaccine Translational Research Branch (VTRB). The drug product was filled and released by the Dale and Betty Bumpers Vaccine Research Center (VRC) and Vaccine Clinical Materials Program (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.

- VRC-HIVMAB075-00-AB (VRC07-523LS) is a human mAb that targets the HIV-1 CD4 binding site. It was developed by the VRC/NIAID/NIH and manufactured under current Good Manufacturing Practice (cGMP) standards at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program, 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 and 3 mL glass vials with a 2.25 mL ± 0.1 mL fill volume.

Table 1-1 Schema

Study arm	Number	Dose	Route	Month 0 (Day 0)	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					

Notes

IV = intravenous infusion; SC = subcutaneous infusion. Infusions are given sequentially in the order shown.

[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

Participants

32 healthy, HIV-1–uninfected volunteers aged 18 to 50 years

Multicenter design

Part A: dose escalation, first in human, open-label IV or SC product administration with randomization into Groups 3 and 4

Part B: randomized, open-label IV or SC product administration

Duration per participant

Part A: 8 months per participant in Groups 1, 2 and 3; 6 months per participant in Group 4; 16 months per participant in Part B.

Estimated total study duration

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

Investigational New Drug (IND) sponsor

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

Study product providers

- PGT121.414.LS: Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, MD, USA)

- VRC07-523LS: Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, MD, USA)

Core operations

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

HIV Prevention Trials Network (HPTN) Leadership Operations Center (LOC), FHI 360 (Durham, North Carolina, USA)

Statistical and data management center (SDMC)

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

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)
- Fred Hutch/University of Washington (Seattle, Washington, USA)
- Dartmouth College (Hanover, New Hampshire, USA)

Study sites

HVTN and HPTN Clinical Research Sites (CRSs) in the United States to be specified in the Site Announcement Memo

Safety monitoring

HVTN 136/HPTN 092 Protocol Safety Review Team (PSRT); HVTN Safety Monitoring Board (SMB)

1.1 Protocol Team

Protocol leadership

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HPTN Community Advisory Board member	W Scott Cooley UNC Chapel Hill CAB	*HPTN community educator/recruiter*	Noshima Darden-Tabb UNC Chapel Hill
HVTN Community engagement unit representative	Gail Broder HVTN Core, Fred Hutch	*HVTN Technical editor*	Richa Chaturvedi HVTN Core, Fred Hutch
HVTN community educator/recruiter	Machel Hunt Emory Hope Clinic		

2 Ethical considerations

It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of these clinical trials. The HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (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 infection, 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.

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

- The Networks require that all international Network sites lacking national plans for providing antiretroviral therapy (ART) develop plans for the care and treatment of participants who acquire HIV infection during a trial. Each plan is developed in consultation with representatives of host countries, communities from which potential trial participants will be drawn, sponsors, and the Networks. Participants who become HIV-infected during the trial are referred to medical practitioners to manage their HIV infection and to identify potential clinical trials they may want to join. If a program for ART provision is not available at a site 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 recognize the importance of institutional review and 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.

The sections below address each of the review concerns by IRBs/ECs and any applicable REs regarding how the research will be conducted.

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 at birth); 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 healthy participant 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 site is provided training in informed consent by the Networks as part of its entering the Network. 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 HVTN 136/HPTN 092 PSRT. In addition, the HVTN 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 his/her private life and the right to control access to individually identifiable information about him/her. 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 (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 the United States, research participants in Network protocols are protected by a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form. In addition, each staff member at each study site 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 site participating in the protocol is required to have a standard operating procedure on how the staff members will protect the confidentiality of study participants.

4 Background

In 2017, more than 35 million people were living with HIV, and 1.8 million people were newly infected with the virus (4). While many countries have achieved progress toward leveling HIV incidence over the past several years, micro-epidemics of infection continue to occur in all regions, even in countries with robust public health infrastructure. Effective biomedical interventions are urgently needed to reduce HIV acquisition. A vaccine is the preferred intervention (5) but remains a major challenge. Antiretroviral treatment can decrease HIV transmission (6) and the use of pre-exposure prophylaxis (PrEP) can decrease acquisition (7), but both interventions face limitations due to adherence, side effects and the logistics and costs of implementation (8). Alternative interventions are being considered that use passively administered, long-acting antiretroviral drugs or neutralizing antibodies (nAb) for prevention (9-14)

Passive immunization for prevention of infectious diseases has been employed for more than 100 years, most often as postexposure prophylaxis against hepatitis A and B, rabies, measles, and varicella zoster virus (15). Palivizumab, a monoclonal antibody (mAb) directed against the F protein of respiratory syncytial virus (RSV), has been used for nearly 2 decades as RSV prophylaxis in preterm and other high-risk infants (16-18). Administration of palivizumab serves as a model for the use of mAbs to block a mucosally-acquired infection.

The most promising approach for applying passive immunization to HIV-1 involves broadly neutralizing antibodies (bnAbs). These naturally occurring antibodies (Abs) may be isolated from many HIV-1–infected individuals, usually after at least several years of infection (19), and feature unusual characteristics, such as long hypervariable loops, an ability to overcome host tolerance control, interaction with glycans, and high levels of somatic mutation in the variable domains facilitating binding to the highly glycosylated HIV-1 envelope protein (20-22). These distinctive features are selected for during natural infection and co-evolution of the virus and antibodies in an infected host; potency and heterologous breadth is acquired over long term iterative cycles of immune escape, epitope diversification, and antibody adaptation to resistant variants (23).

While it is challenging to emulate these processes by vaccination, using bnAbs to inform and expedite the development of HIV vaccines may eventually enable elicitation of such antibodies by immunization (24-29). Meanwhile, there is great interest in studying passive immunization with monoclonal antibodies (mAbs) modeled on these naturally-occurring bnAbs to prevent, treat, and potentially cure HIV-1 infection.

Until recently, these antibodies were few in number, targeted a narrow spectrum of HIV strains and Env epitopes, and were not potent enough for practical use. Since 2012, the field has changed dramatically: new developments in antigen-specific memory B cell sorting and high throughput single-cell polymerase chain reaction (PCR) amplification have led to the isolation of new monoclonal antibodies with extraordinary potency and breadth (11, 12, 30).

In 2016, VRC01 advanced to the first prevention efficacy trials in HIV-uninfected individuals. In addition to assessing safety and PK, the Antibody Mediated Prevention (AMP) Trials (HVTN 704/HPTN 085 [NCT02716675] and HVTN 703/HPTN 081 [NCT02568215]) include assessment of neutralizing and non-neutralizing antiviral activity (ie, Fc effector functions), neutralization and genetic sieve analyses, and correlates analyses (31). These important proof-of-concept trials will help us determine whether antibodies that neutralize HIV-1 in vitro and protect nonhuman primates (NHPs) from experimental simian-human immunodeficiency virus (SHIV) challenge will protect against the acquisition of HIV infection in humans. They also aim to determine the protective titer – a critical parameter in designing future clinical trials of passive immunization and vaccines.

As of 2019, dozens of bnAbs have been identified, and their HIV-1 target sites and mechanisms of neutralization have been elucidated (20, 21, 23, 24, 32, 33). These efforts have set the stage for evaluation of these antibodies' potential to contribute to HIV-1 prevention, treatment, and possibly cure (25-29). Passive infusion studies in NHPs demonstrated that bnAbs were effective in protection against mucosal SHIV challenge (34-43) and broadly neutralizing investigational mAb products can reduce HIV RNA levels in humans (43-50). Results from early-phase human clinical trials using different classes of bnAbs, such as those targeting the CD4 binding site (eg, VRC01 and 3BNC117) and a glycan-dependent epitope at the base of the V3 loop (eg, 10-1074 and PGT121), have been encouraging, demonstrating the potential for and challenges of developing anti-HIV-1 bnAbs as preventive and therapeutic agents (41, 44-47, 49-51).

4.1 Rationale for trial concept

The development of mAb investigational products for the potential prevention and treatment of HIV is evolving rapidly. Multiple mAbs have been developed, each of which target 1 of 6 known sites on the HIV-1 Env protein (Figure 4-1):

1. the CD4-binding site,
2. V2-apex region of gp120,
3. V3-glycan region of gp120,
4. the membrane-proximal external region (MPER) of gp41,
5. the gp120-gp41 interface/gp41 fusion peptide,
6. glycan-dependent epitopes in the center of the gp120 silent face (52).

These mAb products display a broad range of neutralization potency and breadth and some of the more promising molecules have been engineered for improved neutralization, manufacturability, stability, and serum half-life. Additional improvements continue to be made, including the construction of engineered, chimeric bi- and tri-specific mAbs (53-55). While relatively few HIV neutralizing mAbs are currently available for clinical evaluation, those that are include some of the broadest and most potent mAbs identified to date. Thus, the available products, though limited, provide opportunities to address important scientific

questions through clinical evaluation and to plan for follow-up efficacy trials of passively delivered mAbs.

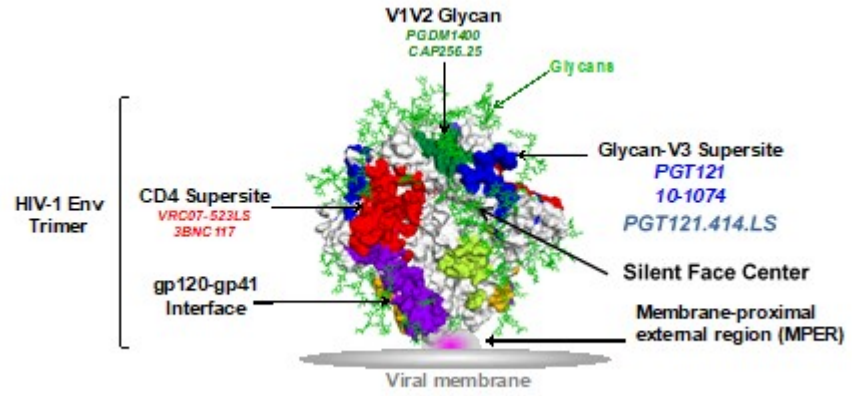

Figure 4-1 Antibody targets on the HIV-1 trimer (image by Stewart-Jones, Doria-Rose, Stuckey; adapted from (56, 57))

As mentioned above, the VRC01 AMP trials are important proof-of-concept trials to demonstrate whether bnAbs can prevent HIV infection, and to gain insights into the potency needed for prevention. However, we recognize that much stronger and broader neutralization will be required to counter the genetic variability of HIV across diverse geographic locations. Indeed, models that combine in vitro neutralizing activity and NHP protection data predict that 2 or more of the best bnAbs may be needed, either as a combination of individual bnAbs, as bi- or tri-specific bnAbs, or both (13).

The overarching aims guiding this study are to characterize the safety, tolerability, and PK of 2 broadly-neutralizing mAb investigational products, VRC07-523LS (CD4-binding site) and PGT121.414.LS (V3-glycan), when co-administered IV and SC, and to describe whether there is an increase in neutralization potential in humans with this mAb combination as predicted by the in vitro neutralizing activity of the corresponding non-infused clinical products. The data collected in this protocol will contribute significantly to future analyses that aim to combine LS versions of 3 broadly-neutralizing mAbs to optimize prevention efficacy.

Our long-term goal is to clinically test the combination of VRC07-523LS, PGT121.414.LS and PGDM1400LS because of the superior in vitro neutralization profiles across all major global subtypes (see below). If efficacious, this combination would likely be developed as a global product. Data collected in this protocol will contribute significantly to this end goal.

It is reasonable to ask why we are working to advance these specific mAbs from among the various options available. CD4-binding site bnAbs are likely going to serve as the “backbone” of any mAb combination approach, owing to their exceptional breadth. VRC01 has detectable inhibitory concentration (IC80) responses for 80% of the 403 globally sampled pseudoviruses summarized in

Figure 4-2, with a median IC80 of 1.75 mcg/mL. Ongoing clinical studies have begun to assess VRC07-523LS, which has substantially improved performance in vitro, neutralizing up to 97% of circulating strains, with a median IC80 of only 0.162 mcg/mL. Among all of the diverse pseudoviruses with neutralization data collected in the Los Alamos Immunology database (Compile, Analyze and Tally nAb Panels [CATNAP]), 59% (412 of 704) have an IC50 < 1 mcg/mL using VRC01, while 91% (365/402) have an IC50 < 1 mcg/mL using VRC07-523LS (www.hiv.lanl.giv/components/sequence/HIV/neutralization/index.html).

V3-glycan and V2-apex bnAbs have a narrower breadth than CD4-binding site bnAbs, but their potency often exceeds CD4-binding site Abs for a subset of viruses (Figure 4-2). V3-glycan and V2-apex bnAbs are also complementary in coverage (42), individually neutralizing 50-70% of viruses – whereas combined, they neutralize >90% of viruses at IC50 < 1 mcg/mL. Studies of in vitro neutralization have shown that a triple combination of CD4-binding site + V2-apex + V3-glycan bnAbs outperforms "best-in-class" single and dual bnAbs, while the addition of a fourth bnAb provides minimal additional benefit in terms of enhancing the predicted combined IC50 values (13, 14, 58). Such a triple combination also increases the chance that at least 2 of the 3 antibodies in the combination will be simultaneously active (dual coverage) on any given strain. This in turn diminishes the chance for rapid selection of immune escape variants following exposure. Dual coverage also accounts for differences in PK among the antibodies, and for differences in the neutralization profiles of circulating viruses and the complex viral quasispecies encountered at transmission (42), to improve the probability that at least 1 bnAb will be active at an effective concentration over an extended period of time between dosing intervals.

With respect to other "categories" of bnAbs, those targeting the gp120-gp41 interface/fusion peptide and the gp120 silent face are not currently being pursued for passive prevention but remain of interest for vaccine design (59). Such antibodies may have benefits in clade A and B epidemics (60) MPER bnAbs exhibit promising potency and breadth but often possess lipid-binding properties that could have undesirable effects. In a recent trial, the lead MPER bnAb clinical candidate, 10E8VLS, had a disappointing PK profile, and 1 participant who received subcutaneous injections experienced severe erythema and panniculitis at the injection site, resulting in suspension of the trial (61). It is possible that MPER or fusion peptide-targeting bnAbs may eventually be useful as clinical products, but are currently not ready for evaluation.

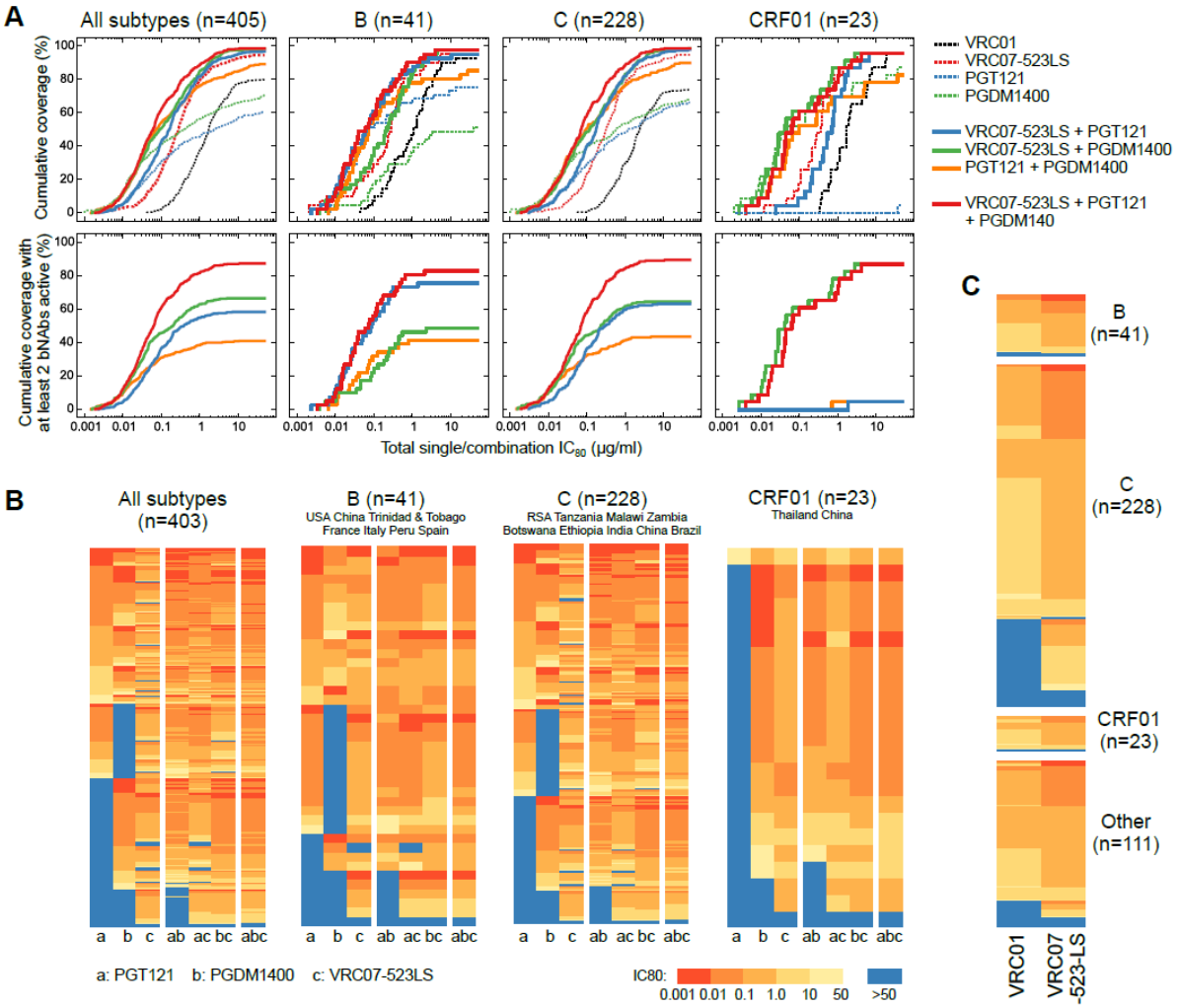

Figure 4-2 Magnitude, breadth and dual coverage predictions for PGT121, PGDM1400, VRC07-523LS and combinations of these 3 mAbs against a multiclade panel of HIV isolates. VRC01 is shown as reference to AMP. (A) The top row shows cumulative coverage (%) of pseudoviruses at a given IC80 for single bnAbs and their 2 and 3 bnAb combinations. The bottom row shows cumulative coverage (%) of pseudoviruses neutralized by at least 2 bnAbs in the 2 or 3 bnAb combinations as a function of combination IC80 titers. (B) IC80 titers for individual bnAbs and their 2 and 3 combinations for the full dataset and for individual subtypes of interest. Rows indicate pseudoviruses and columns indicate IC80 titers for a given bnAb or combination. For each panel, the ordering of viruses is the same between single bnAbs and 2/3 bnAb combinations. USA = United States, RSA = South Africa. (C) IC80 titers for VRC01 and VRC07-523LS are shown as heatmaps, as in (B). Pseudoviruses are grouped according to subtypes of interest, with "Other" indicating all other subtypes in the dataset.

PGT121.414.LS was recently assayed by the VRC against a multiclade panel of 208 viruses and shown to be equivalent to PGT121 against most but not all of the viruses (Figure 4-3). In some cases PGT121.414.LS had diminished potency against a subset of viruses that are least sensitive to PGT121, whereas it gained potency against a subset of viruses that are most sensitive to PGT121. Despite these differences, there was excellent overall concordance between the 2 antibodies (r2= 0.736 and 0.776 for IC50 and IC80 values, respectively,

p<0.0001). These findings support the use of PGT121 neutralization data to predict PGT121.414.LS activity.

As shown in Figure 4-3, PGT121 displays limited breadth but has outstanding potency against the viruses that are neutralized, having among the lowest median IC50 and IC80 titers among all bnAbs identified to date (30) (see Section 4.2.1). VRC07-523LS, a highly engineered derivative of the bnAb VRC01, displays somewhat lower potency than PGT121 but has outstanding breadth and an improved PK profile (see Section 4.2.2).

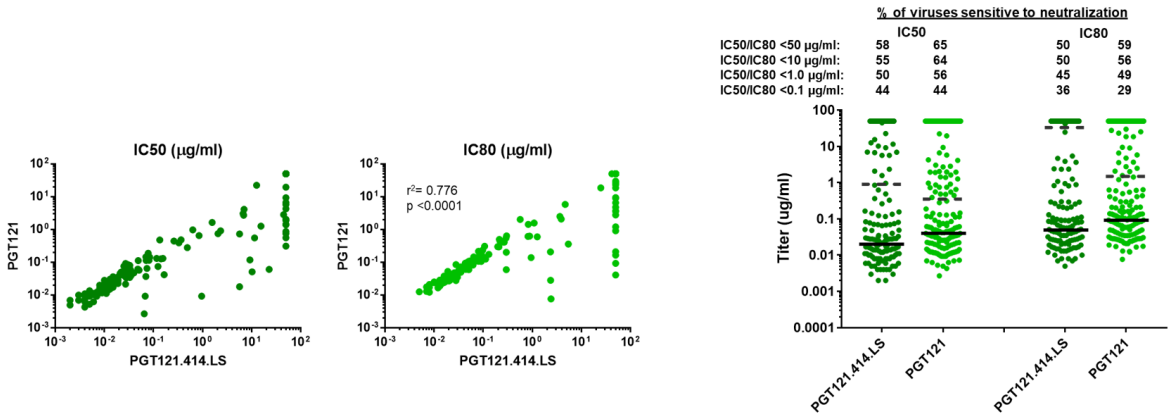

Figure 4-3 Comparison of in vitro neutralizing activity of PGT121 and PGT121.414.LS against a multiclade pseudovirus panel (n=208). 50 mcg/mL was the highest concentration tested and is used as the cut-off for negative neutralization. Dotted line shows median IC50 and IC80 of all viruses (including those not neutralized). Solid line shows median IC50 and IC80 of viruses sensitive to neutralization (excluding those not neutralized). Data courtesy of the Vaccine Research Center, NIH.

Modeling by Korber, Wagh, and colleagues, using PGT121 in vitro data and the predicted neutralizing activity of PGT121.414.LS based on PGT121 data, suggests that the addition of PGT121.414.LS provides enhanced breadth and potency of heterologous variants relative to VRC07-523LS alone. In particular, 22 of the 403 pseudoviruses tested for neutralization had no detectable sensitivity to VRC07-523LS, and of these 9 were sensitive to PGT121. Perhaps more importantly, for 37% of the 403 pseudoviruses tested, PGT121 was more potent than VRC07-523LS, so it often makes a very substantial contribution to the overall potency of the combination (Figure 4-3). The combination of VRC07-523LS + PGT121.414.LS is predicted to provide no dual coverage of CRF01 because of broad resistance of this subtype to PGT121. PGT121 also has far more limited activity against clade A and CRF02, common viral lineages in west and central Africa. Thus, while in vitro neutralizing activity suggests that VRC01-523LS + PGT121.414.LS has potential for success in subtype B populations where both antibodies tend to be highly active (Figure 4-2) the addition of a V2-apex class antibody (eg, PGDM1400LS), because of complementary coverage with PGT121.414.LS and complementary potency with VRC07-523LS, would be the best candidate for a third bnAb addition.

Early product development assessment of the PGT121 and VRC07-523LS mAbs has revealed an attractive product profile, including safety

and tolerability in early human trials (10, 45-47). Given the available safety and tolerability data of these 2 mAbs, it is scientifically sound to evaluate PGT121.414.LS alone and in combination with VRC07-523LS in a phase 1 human clinical trial to assess safety (including anti-drug antibodies [ADA]), PK, and functional activity, and to contribute to the development of an experimental platform for a triple bnAb combination. This approach for optimizing future combination products is similar to the approach taken to develop combination therapies for HIV. The combination of these 2 mAbs with distinct epitope specificities will provide valuable experience assessing the potential additive, synergistic, or antagonistic properties of 2 bnAbs administered sequentially at the same study visit.

Taken together, data collected in this protocol will contribute significantly to future analyses and to the design of future studies seeking to optimize mAb combinations for HIV-1 prevention.

4.1.1 Cross-network implementation

DAIDS has requested that its two 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 two 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 Study products

4.2.1 PGT121.414.LS

PGT121.BIJ414.LS (referenced and labeled as PGT121.414.LS) was produced by Just Biotherapeutics in collaboration with Dan Barouch (Beth Israel Deaconess Medical Center), and collaborative engagement of CAVD investigators. The drug substance was manufactured under cGMP standards at Just Biotherapeutics under contract to DAIDS's Vaccine Translational Research Branch (VTRB). The drug product was filled and released for the Dale and Betty Bumpers Vaccine Research Center (VRC) by the Vaccine Clinical Materials Program (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 heavy chain are the Xencor Xtend LS modifications helping provide a significantly reduced elimination half-life in vivo (62, 63). The magnitude and breadth of neutralizing activity of PGT121.414.LS and its PGT121 in vitro were shown to be nearly equivalent against a multiclade panel of Env-pseudotyped viruses (Figure 4-3).

The bnAb, 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 (64-66). 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 (30). 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 (30, 67, 68).

4.2.2 VRC07-523LS (VRC-HIVMAB075-00-AB)

VRC07-523LS is a human mAb targeting the HIV-1 CD4 binding site, developed by NIAID-NIH at the VRC. A similar antibody, VRC01, also targeting the CD4 binding site, is currently in clinical trials for both HIV-1 prevention (IND 113,611 and IND 125,494) and therapeutic (IND 126,001, IND 126,664, and IND 113,017) indications. VRC01 was originally isolated from a subject infected with HIV-1 for more than 15 years whose immune system controlled the virus without ART (69, 70). Through advances in B-cell immunology, cloning, and structure-guided optimization techniques, numerous HIV-1 neutralizing mAbs, including VRC07 (“07” denotes sequential numbering when discovered), were isolated and subsequently engineered to have potency and breadth greater than those of earlier antibodies (36). This protocol will use VRC07-523LS (“523” denotes sequential numbering when the engineered variant was generated; “LS” denotes 2 amino acid mutations).

The VRC07 (wild-type) heavy chain was identified by 454 deep sequencing based on its similarity to VRC01 and was then engineered to pair it with the VRC01 (wild-type) light chain. The mutations that together define the 523 designation are a glycine-to-histidine mutation at residue 54 of the heavy chain, a deletion of the first 2 amino acids, glutamate and isoleucine, from the light chain, and a valine-to-serine mutation at the third amino acid residue of the light chain (36). The LS designation in VRC07-523LS specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of

the heavy chain constant region. The LS mutation was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor (FcRn); this mutation increases the recirculation of functional immunoglobulin G (IgG) (40, 62), thus, increasing plasma half-life.

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 (36). In addition, it displayed minimal levels of autoreactivity.

4.3 Trial design rationale

This 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 pharmacokinetics of PGT121.414.LS with and without VRC07-523LS, a CD4 binding site mAb. The hypothesis is that PGT121.414.LS alone and paired with VRC07-523LS will be safe for administration to healthy adults by both the IV and SC routes.

In Part A of the study, PGT121.414.LS will be 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 will have 3 participants. At each of 3 visits in Part B of the study, participants will receive consecutive administration 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). Each group in Part B will have 10 participants, yielding a total sample size for Parts A and B of 32. Participants will be 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.

Cumulative safety data will be reviewed on a daily basis by Network clinical safety staff (ie, Clinical Safety Specialist nurses and physicians) and reviewed at least weekly by the HVTN 136/HPTN 092 Protocol Safety Review Team (PSRT) for all participants in all groups. There will be a planned safety hold to evaluate safety at least 2 weeks after product administration in all groups (see Section 11.3.1 and Table 11-1).

The HVTN 136/HPTN 092 PSRT will request an ad hoc review of the data by the HVTN SMB in the instance that serious safety events are identified during the planned safety holds (see Section 11.3).

Ideally, this study will demonstrate that PGT121.414.LS alone and in combination with VRC07-523LS is safe and well-tolerated when given intravenously and subcutaneously, and that the half-life of PGT121.414.LS is significantly extended compared to PGT121, as well as unchanged by co-administration with VRC07-523LS. The study aims to evaluate if sera from infused participants retain the same neutralizing breadth in vitro as PGT121 alone and in combination with VRC07-523LS.

This protocol is part of a series of protocols gathering data to determine the best mAb combinations to be used in a future efficacy trial. The doses and dosing intervals selected for this trial will allow for comparability with other clinical trials evaluating VRC07-523LS and PGT121 both of which are being administered alone and in different combinations. Existing clinical trials evaluating VRC07-523LS and PGT121 either alone or in combination are summarized in Table 4-1.

Table 4-1 Summary of bnAb clinical trials that evaluate VRC07-523LS and PGT121 alone or in combination.

Study	bnAb	Dose (mg/kg) and Route	Interval(weeks)
VRC605	VRC07-523LS	1,5,20,40 IV	Single dose
		5 SC	Single dose
		5 SC	Q12
		20 IV	Q12
HVTN 127/ HPTN 087	VRC07-523LS	2.5,5,20 IV	Q16
		2.5,5 SC	Q16
		2.5 IM	Q16
IAVI T001	PGT121	3,10,30 IV	Single dose
		3 SC	Single dose
IAVI T002	PGT121+PGDM1400	3+3 IV	Single dose
		10+10 IV	Single dose
		30+30 IV	Single dose
IAVI T003	PGT121+VRC07-523LS	30+30 IV	Single dose
	PGT121+VRC07-523LS+ PGDM1400	20+20+20 IV	Single dose
HVTN 130/ HPTN 089	PGT121+VRC07-523LS	20+20 IV	Single dose
	PGT121+PGDM1400+ VRC07-523LS	20+20+20 IV	Q16

IV = intravenous infusion
SC = subcutaneous injection
IM = intramuscular injection

The safety, tolerability, pharmacokinetics, and antiviral activity of VRC07-523LS and PGT121 are being evaluated, individually and in some combinations, in ongoing clinical trials (see Section 4.6). Currently, data for VRC07-523LS from VRC 605 (NCT03015181) are being analyzed. The HVTN 127/HPTN 087 study (NCT03387150), which enrolled participants from February to October 2018, is gathering additional data on this mAb (see Section 4.6).

Additionally, IAVI T001 (NCT02960581) is assessing PGT121 alone, IAVI T002 (NCT03205917) is gathering data on PGT121 administered in combination with PGDM1400 (10, 45-47) and IAVI T003 (NCT03721510) is evaluating PGT121 administered in either a dual combination with VRC07-523LS or a triple combination with VRC07-523LS and PGDM1400 (see Section 4.6).

Furthermore, the HVTN 130/HPTN 089 study is designed to gather safety information on the dual combination groups (PGT121+VRC07-523LS) and in the triple combination Group (PGDM1400+PGT121+VRC07-523LS). The HVTN 130/HPTN 089 protocol opened in July 2019 (see Section 4.6).

4.3.1 Dose, schedule and route of administration

The doses and dosing schedule to be used in the HVTN 136/HPTN 092 clinical trial were selected based on prior clinical experience with VRC07-523LS and PGT121, as well as on PK modeling using nonclinical and clinical data for VRC07-523LS and PGT121.

The proposed doses for Groups 1, 2, and 3 in Part A (3, 10 and 30 mg/kg IV), were selected based on previously tested doses of PGT121 in preclinical studies and in the IAVI T001 and IAVI T002 clinical trials. Because PGT121.414.LS is formulated in higher concentrations than PGT121, it is possible to administer a higher dose (5 vs. 3 mg/kg) via the SC route.

Part A has a dose-escalation design, starting at the same low dose of antibody (3 mg/kg IV) that was used as a starting dose in IAVI T001, the first in human trial of PGT121.

In Part B, dosing is scheduled every 16 weeks based on preclinical and clinical data of VRC07-523LS and PGT121. The choice of 20 mg/kg dose IV and 5 mg/kg SC aligns with ongoing protocols using VRC07-523LS either alone (VRC605 and HVTN 127/HPTN 087) or in combination with PGT121 (IAVI T003 and HVTN 130/HPTN 089).

The doses of VRC07-523LS in Part B were selected using model-based predictions of this mAb serum concentration over time following IV and SC administrations of VRC07-523LS. Predictions were generated through simulations of PK data on VRC07-523LS serum concentrations based on a PK model of the VRC605 study. Moreover, dose and dosing intervals of 16 weeks in Groups 5 and 6 were selected to have high probability of achieving a trough above 1 mcg/mL for VRC07-523LS and likely for PGT121.414.LS (Figure 4-5), where 1 mcg/mL was shown to provide excellent coverage of the bnAb combination against a broad panel of viruses in vitro (Figure 4-2).

An additional benefit to testing low doses of PGT121.414.LS, particularly the 5 mg/kg SC dose, is to collect PK data at low concentrations where this product may still have antiviral activity. Data from the IAVI T001 trial have shown that the antibody PGT121 has very high potency in humans, with suppression of virus in HIV infected individuals (off all antiretrovirals) at concentrations < 0.7 mcg/mL. Therefore, it would be important to know the PK parameters of the antibody at these very low concentrations. This window of the concentration-time profile is more likely to be captured following low dose administrations, given the more frequent sampling following product administration. Characterizing low concentrations could be missed following the high dose administration as these

are likely to occur when sampling is sparse, with the possibility that concentrations fall below the limit of quantification between visits.

Moreover, Figure 4-4 shows the predicted serum concentrations of VRC07-523LS following multiple IV infusions at 20 mg/kg or multiple SC injections at 5 mg/kg every 8 to 20 weeks. These concentrations were simulated based on population PK models using PK data observed in VRC605 for VRC07-523LS.

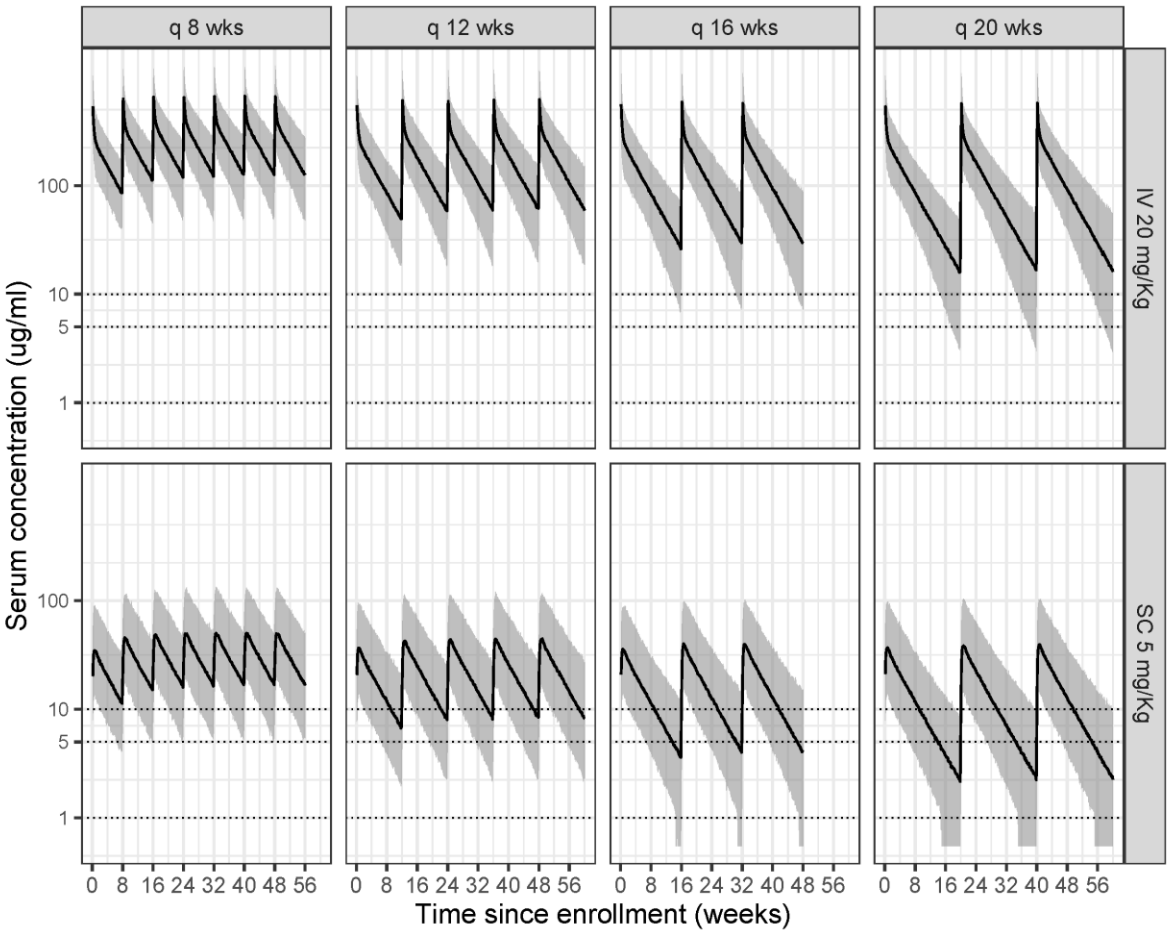

Figure 4-4 Predicted VRC07-523LS concentration with multiple 8- to 20-weekly IV infusions at 20 mg/kg or SC injections at 5 mg/kg. Shown are median (solid lines), 5th and 95th percentiles (shaded areas) of predicted drug levels with values truncated at 0.55 mcg/mL.

In these simulations, the body weights of hypothetical trial participants were randomly drawn with replacement from the sample of body weights collected in the HVTN 104 study of VRC01 in US sites, some of which will be used in this study (71, 72). In addition, linear PK was assumed for the VRC07-523LS so that PK parameters estimated based on single-dose settings carried forward to multiple-dose settings. The PK parameters used in the simulations were estimated based on observed serum concentration data for VRC07-523LS at 5, 20, and 40 mg/kg following a single IV infusion, at 20 mg/kg following three 12-weekly IV infusions, at 5mg/kg following a single and at 5 mg/kg following three 12-weekly

SC injections. The mean and variance of log-transformed serum concentrations were computed after each IV infusion. Specifically, after the third IV infusion of VRC07-523LS at a dose level of 20 mg/kg, the mean serum concentrations were predicted to be 28.5, 9.0, and 2.8 mcg/mL, respectively at 16, 24, and 32 weeks post infusion. After the third SC injection at a dose level of 5 mg/kg, the mean serum concentration was predicted to be 3.9, and 1.2 mcg/mL, respectively, at 16 and 24 weeks post injection. In addition, the chance of observing trough serum concentrations that are greater than 1 mcg/mL at 16 weeks post product administration is >95% for both 20 mg/kg IV and 5 mg/kg SC VRC07-523LS. Given the IC50 and IC80 data of the mAbs, these PK simulation results suggest that the proposed study design should be able to attain desirable serum concentration levels over time that confer sufficient neutralization against diverse panels of viruses (see Section 6.1). Thus, based on currently available data, in Groups 5 and 6, a dosing interval of every 16 weeks was selected to have high probability of achieving a trough above 1 mcg/mL for VRC07-523LS, and likely for PGT121.414.LS. This threshold of 1 mcg/mL is the limit of detection of the currently used anti-idiotypic enzyme-linked immunosorbent assay (ELISA) for mAb serum concentrations.

Substantial safety data have already been collected over several trials on products related to VRC07-523LS, including VRC01 and VRC01LS. These studies have demonstrated the safety and tolerability of the IV administration of each of these individual mAbs at doses similar to or greater than those proposed in this study. For example, in VRC 606 (NCT02599896), the doses for VRC01LS in HIV-uninfected participants ranged between 1 and 40 mg/kg for IV administrations. Moreover, in multiple studies, including VRC 601, VRC 602, HVTN 104, RV397, RV398, A5340, A5342, and P1112, doses for VRC01 in HIV-uninfected and/or HIV-infected participants ranged between 1 and 40 mg/kg for IV administrations.

Given the reassuring safety profile of VRC07-523LS, PGT121, and similar mAbs given via IV and SC routes in previous studies and ongoing trials evaluating these mAbs either individually or in combination (see Section 4.6), placebo recipients are not included in this trial.

4.4 Plans for future product development and testing

This protocol is part of a path to an efficacy trial of a triple bnAb combination comprising CD4-binding site + V2-apex + V3-glycan bnAbs. The CD4 binding bnAb (VRC07-523LS) will serve as the “backbone” for future dual- and triple-combination mAb regimens. This protocol complements HVTN 130/HPTN 089 in a series of studies that will evaluate synergism and antagonism between mAbs targeting different epitopes on HIV, with respect to PK, neutralization breadth, and potency. HVTN 130/HPTN 089 is testing the combination of VRC07-523LS and non-LS versions of PGT121 and PGDM1400. It is expected that future studies will evaluate mAb combinations incorporating LS-modified versions of all 3 antibodies in preparation for a planned efficacy trial. HVTN 136/HPTN 092

will provide the foundation for combining LS versions of 2 bnAbs to different epitopes as a platform for adding the LS version of a third complementary bnAb in the future. The third planned bnAb, PGDM1400LS, is not expected to be ready for first-in-human (FIH) clinical testing until mid-to-late 2020. In the meantime, it is important to establish the behavior of VRC07-523LS and PGT121.414.LS when co-administered intravenously and subcutaneously, to determine whether co-administration alters the expected safety, tolerability, PK and neutralizing activity of the products compared to when they are administered as single agents.

Other mAb interventions for HIV-1 in the clinical pipeline include:

1. Trispecific antibody SAR441236 (Sanofi), incorporating Fab portions of VRC01, 10E8v4, and PGDM1400 along with an LS modification, which will undergo phase 1 clinical testing in HVTN 129/HPTN 088
2. Bispecific 10E8.4/iMab (ADARC/Gates) that began phase 1 testing in early 2019
3. Dual combination of 3BNC117LS (CD4-binding site) and 10-1074LS (V3-glycan) slated to begin phase 1/2 testing in the second half of 2019 (Rockefeller University/IAVI/Gates), and
4. Dual combination of VRC07-523LS and CAP256LS for South Africa, (VRC/CAPRISA).

The unique dual combination of VRC07-523LS + PGT121.414.LS in HVTN 136/HPTN 092 will provide critical information to guide future trials of mAbs incorporating LS-modified versions of a V2-apex bnAb (eg, PGDM1400LS). This triple combination is expected to have favorable safety, tolerability and PK, and to be superior to VRC01 for protection efficacy against multiple genetic subtypes of HIV-1 in different parts of the world.

4.5 Preclinical studies

4.5.1 Preclinical studies of PGT121

PGT121 has been assessed in a non-Good Laboratory Practice (GLP) pharmacokinetic rat study, a GLP in vitro tissue cross-reactivity study (TCR), and a GLP repeat-dose toxicity study in rats. In the repeat-dose toxicity study, animals were given 30 mg/kg or 300 mg/kg intravenously or 30 mg/kg subcutaneously at weekly intervals over a 28-day period. There were minor disturbances in the plasma proteins with higher total protein, albumin and globulin resulting in a lower albumin/globulin ratio. There was also transient local microscopic inflammation (fibrosis, mixed cell inflammation) at the injection site following subcutaneous administration, which increased in severity and/or incidence compared to the control animals. The findings resolved after a 4-week treatment-free period. The no-observed-adverse-effect-level (NOAEL) for intravenous administration was 300 mg/kg and for subcutaneous injection was 30 mg/kg, which were the highest dose levels administered.

PGT121 can neutralize a wide array of HIV-1 viruses in vitro and can treat and prevent simian human immunodeficiency virus (SHIV) in the NHP model.

Complete protection from different strains of SHIV was shown with 20 mg/kg and protection in most animals at levels of 5 mg/kg, 1 mg/kg, and 0.2 mg/kg. PGT121 administered at 10 mg/kg to SHIV-infected animals resulted in rapid virological control to undetectable levels by day 7 followed by viral rebound between day 42 and day 56 in 3 of the 4 animals after antibody levels declined to undetectable. One animal exhibited long-term control (73).

4.5.2 Preclinical studies of PGT121.414.LS

Preclinical studies of PGT121.414.LS include: humanized FcRn mouse PK, NHP PK, repeat dose toxicity and Tissue Cross Reactivity.

4.5.2.1 Pharmacokinetic study of PGT121.414.LS in human FcRn transgenic mice

The Vaccine Research Center (VRC), NIAID, NIH evaluated the in vivo pharmacokinetic profile of PGT121.414.LS in three human FcRn transgenic mice (74-76). In this study, we tested PGT121.414.LS (lot #S-20190121-1) produced from a stably transfected CHO cell line. The antibody was given at a single bolus dose of 10 mg/kg via the intravenous route. The levels of antibody in the sera of these animals at various time points up to 28 days after administration were then quantitated by an anti-PGT121 idiotype based ELISA method. Figure 4-5 shows the sera levels of PGT121.414.LS in each animal, with levels maintained above 10 mcg/mL up to day 9 post infusion 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 anti-drug antibody (ADA) response against PGT121.414.LS in those animals. The third animal showed a longer persistence of the antibody in the sera with levels dropping below the detection limit at day 28 post infusion.

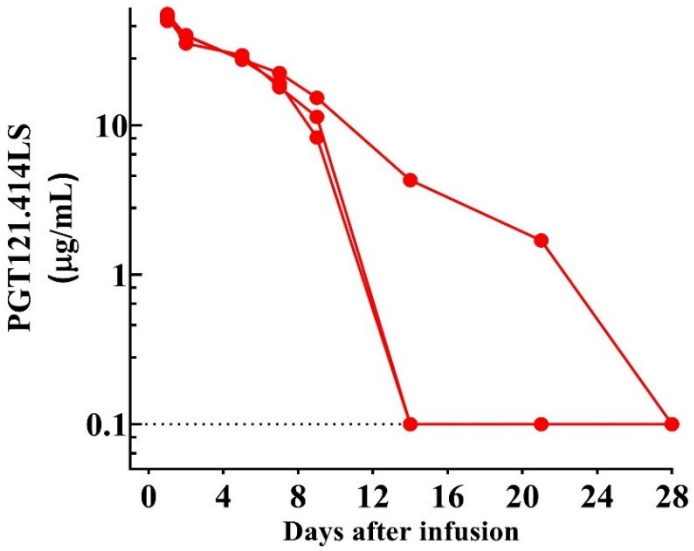

Figure 4-5. Sera levels of PGT121.414.LS antibody in three human FcRn transgenic mice administered 10 mg/kg of the antibody via the intravenous route.

The pharmacokinetic parameters were calculated using a non-compartment model in the WinNonLin software package and are presented in Table 4-2. The average half-life was calculated to be 3.61 days with a range of 2.53 to 4.59 days. The average AUC (Area Under the Curve) was calculated to be 332 Day*mcg/mL with a range of 312 to 368 Day*mcg/mL. The average clearance was calculated to be 15.13 mL/Day/kg with a range of 13.58 to 15.99 mL/Day/kg.

Table 4-2. *In vivo* pharmacokinetic parameters for PGT121.414.LS in human FcRn transgenic mice

Antibody	Animal ID	Half-life Day	AUC Day*mcg/mL	Clearance 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***

4.5.2.2 Pharmacokinetic study of PGT121.414.LS in rhesus macaques

The VRC evaluated the in vivo pharmacokinetic profile of PGT121.414.LS in four male and two female rhesus macaques. In this study, we tested PGT121.414.LS (lot #S-20190121-1) produced from a stably transfected CHO cell line. The antibody was given at a single bolus dose of 10 mg/kg via either the subcutaneous (n=3) or intravenous route (n=3). The levels of antibody in the sera of these animals at various time points up to 105 days after administration were then quantitated by an anti-PGT121 idiotype based ELISA method. Figure 4-6 shows the sera levels of PGT121.414.LS in each animal. The initial sera antibody levels were higher when the antibody was given IV compared to SC, but by day 2 the sera antibody levels were similar in all animals irrespective of route and followed similar distribution over time Also, sera antibody levels were maintained above 5mcg/mL for up to 105 days after dosing in all animals irrespective of route. In addition, none of the animals developed any anti-drug antibody responses against PGT121.414.LS in this study, as there were no steep drops in sera antibody levels over time

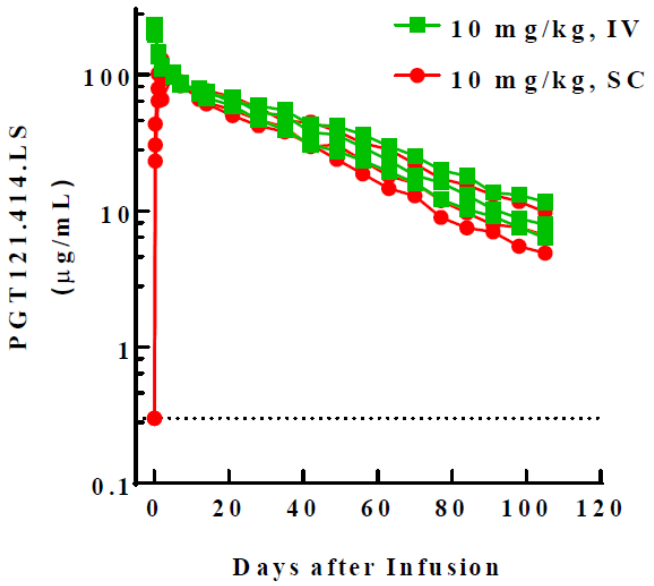

Figure 4-6. Sera levels of PGT121.414.LS antibody in six rhesus macaques administered at 10 mg/kg of the antibody via either the subcutaneous (SC) or intravenous (IV) route.

The pharmacokinetic parameters were calculated using a non-compartment model in the WinNonLin software package and are presented in Table 4-3. 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 clearance was similar between the 2 routes (2.24 mL/day/kg for IV versus 2.61 mL/day/kg for SC).

Table 4-3. *In vivo* pharmacokinetic parameters for PGT121.414.LS in rhesus macaques

Route	Animal ID	Half-life (days)	AUC (day*mcg/mL)	Clearance (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**

Abbreviations: AUC, area under the curve; IV, intravenous; SC, subcutaneous.

4.5.2.3 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 three 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.

4.5.2.4 PGT121.414.LS Tissue Cross Reactivity (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 tissue cross reactivity study. The study details and results are included in the IB.

4.5.2.5 4.5.2.5 PGT121.414.LS preclinical functional studies

PGT121.414.LS was recently assayed against a multiclade panel of 208 Env-pseudoviruses at the VRC (Table 4-4 below). 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 4-4. 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	PGDM 1400	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	PGDM 1400	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 Investigator's Brochure for further details.

4.5.3 Preclinical studies of VRC07-523LS

VRC07-523LS has been assessed in several preclinical safety studies evaluating potential off-target binding, TCR, toxicity, and local tolerance.

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. In addition, it displayed minimal levels of autoreactivity.

In vivo proof-of-concept studies showed that VRC07-523LS is about 5-fold more potent than VRC01LS in Rhesus macaques and displays a longer half-life (9.8 days) than VRC07 (4.9 days) after a single dose of mAb at 10 mg/kg administered intravenously (36).

See the IB for further details.

4.6 Clinical studies

4.6.1 Clinical studies of PGT121

4.6.1.1 IAVI T001

IAVI T001 is a phase 1 randomized placebo-controlled clinical trial of the safety, pharmacokinetics, and antiviral activity of PGT121 in HIV-uninfected and HIV-infected adults. The study design is shown below in Table 4-5.

Table 4-5: 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 hypothesis in IAVI T001 is that PGT121 administration will be safe by both IV and SC routes. The secondary hypothesis is that PGT121 will be detectable in human sera with a definable half-life. As of March 2019, accrual is complete in Groups 1A-1C (HIV-uninfected, 3-30 mg/kg, IV route), Group 1D (HIV-uninfected, 3 mg/kg, SC route), Groups 2A-2C (HIV-infected on ART, 3-30 mg/kg, IV route) and 2B (HIV-infected, 10 mg/kg, IV route), and Group 3A (HIV-infected not on ART, 30 mg/kg IV route). There are 2 remaining slots open for enrollment in Group 3D (HIV-infected off ART with low viral load). Among all participants, there was short-lived, mild or moderate local and systemic reactogenicity. There were no HIV infections, pregnancies or deaths. One participant discontinued early after 10 weeks of follow up. There has been 1 serious adverse event (SAE) that was assessed as not related. The SAE was a case of pre-patellar bursitis occurring 2 months after administration of the

investigational product for which the participant was hospitalized for surgical treatment and IV antibacterials administration for methicillin-sensitive *Staphylococcus aureus* infection. There have been 41 non-serious adverse events, of which 28 were assessed as not related, 9 were assessed as unlikely related (urinary tract infection grade 1, fatigue grade 2, nasal congestion grade 1, headache grade 1, abdominal pain grade 1, CD4+ T-cells decreased grade 1, bruising grade 1, neutropenia grade 1, haematuria grade 1), 4 were assessed as possibly related (gastroenteritis grade 2, fatigue grade 1, fatigue grade 2, headache grade 1). There were no probably related or definitely related adverse events. There were no dose limiting toxicities (DLTs), defined as 1) any grade 3 or greater reactogenicity or adverse event judged by the study investigators as at least possibly related to investigational product, or 2) any SAE considered at least possibly related to investigational product.

PGT121 concentrations have been measured in Group 1A (HIV-uninfected, 3 mg/kg, IV route), Group 1B (HIV-uninfected, 10 mg/kg, IV route), and Group 1C (HIV-uninfected, 30 mg/kg, IV route) by validated anti-idiotype PK and TZM-bl neutralization assays through week 15 postinfusion. As shown in Figure 4-7, the medium half-life of PGT121 during the elimination phase was 23 days, with the half-life ranging from 19 to 26 days. PGT121 neutralizing antibody (nAb) concentrations to X2088_c9 and CNE30 pseudoviruses were significantly and positively correlated with the PGT121 binding Ab concentrations.

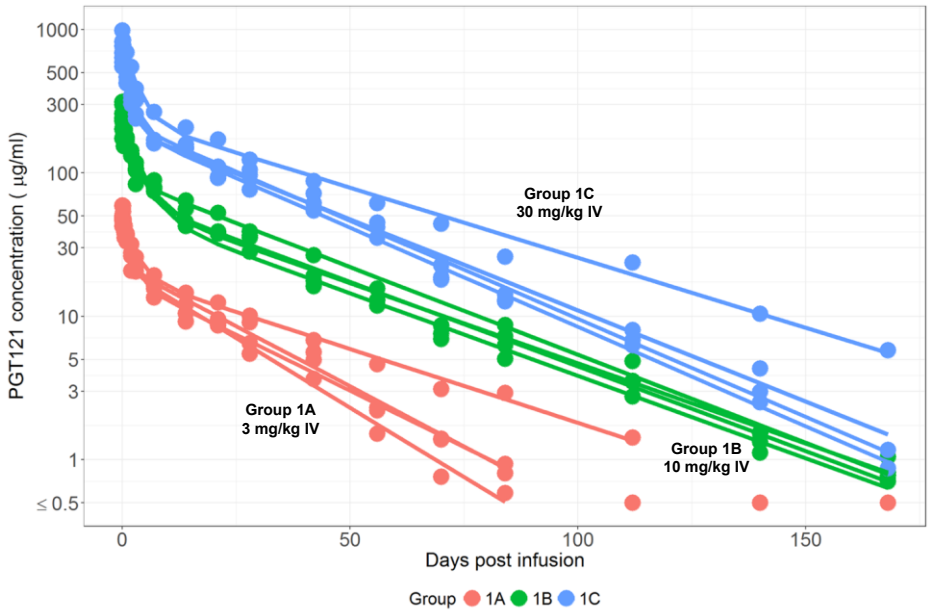

Figure 4-7: PGT121 binding antibody concentrations in Group 1A (HIV uninfected, 3 mg/kg), Group 1B (HIV uninfected, 10 mg/kg), and Group 1C (HIV uninfected, 30 mg/kg).

4.6.1.2 IAVI T002

T002 is a phase 1, randomized, placebo-controlled clinical trial of the safety, pharmacokinetics, and antiviral activity of PGDM1400 as well as the combination

of PGDM1400 and PGT121 in HIV-uninfected and HIV-infected adults. The study design is shown in Table 4-6.

Table 4-6: IAVI T002 study schema

	Group	Participants	Sub-Group	Regimen	N	Dose (mg/kg)
Part 1 – MTD	1	HIV-uninfected participants	1A	PGDM1400/Placebo	3/1 (6/2 if DLT)	3 IV
			1B	PGDM1400/Placebo	3/1 (6/2 if DLT)	10 IV
			1C	PGDM1400/Placebo	3/1 (6/2 if DLT)	30 IV
				Total Group 1	9/3 = 12 (max 18/6 = 24 if DLT)	
	2	HIV-uninfected participants	2A	PGDM1400 + PGT121/Placebo	3/1 (6/2 if DLT)	3 + 3 IV
			2B	PGDM1400 + PGT121/Placebo	3/1 (6/2 if DLT)	10 + 10 IV
			2C	PGDM1400 + PGT121/Placebo	3/1 (6/2 if DLT)	30 + 30 IV
				Total Group 2	9/3 = 12 (max 18/6 = 24 if DLT)	
				Total Groups 1 and 2	18/6 = 24 (max 36/12 = 48 if DLT)	
Safety Monitoring Committee						
Part 2 – antiviral effect	3	HIV-infected off ART (VL $1x10^3$ – $1x10^5$ copies/ml)	3A	PGDM1400	6 (max 18)	MTD IV
			3B	PGDM1400+PGT121	6 (max 18)	MTD IV
				Total Group 3	12 (max 36)	
				Total entire study	36 (max 84)	

DLT, dose limiting toxicity; MTD, maximum tolerated dose

Blinded interim safety data as of March 2019 includes all accumulated safety data for 24 weeks post investigational product administration for Groups 1A-C and 2A-C. After intravenous administration of 3 mg/kg, 10 mg/kg, and 30 mg/kg of PGDM1400 and after administration of 3+3 mg/kg, 10+10 mg/kg, and 30+30 mg/kg of PGDM1400 and PGT121, there was short-lived, mild or moderate local and systemic reactogenicity. There have been no related SAEs. To date, there have been no study safety pauses for adverse events (AEs) and product administrations have been generally well tolerated.

PGDM1400 concentrations have been measured in Group 1A, 1B, and 1C (HIV-uninfected, 3, 10, and 30 mg/kg, IV route, respectively) by validated anti-idiotype PK assays through week 4-24 postinfusion. The preliminary medium half-life of PGDM1400 during the elimination phase is 21 days (Figure 4-8).

As of March 2019 accrual is complete in Groups 1A, 1B, and 1C (HIV-uninfected, PGDM1400 at 3, 10, and 30 mg/kg, respectively, IV route) and in Group 2A, 2B, and 2C (HIV uninfected, PGDM1400+PGT121 at 3+3, 10+10, and 30+30 mg/kg, respectively, IV route). The external Safety Monitoring

Committee (SMC) reviewed the safety data on October 17, 2018. There were no DLTs, defined as: (1) any grade 3 or greater reactogenicity, or any adverse events judged by the study investigators as at least possibly related to investigational product; or (2) any SAE considered at least possibly related to investigational product), and maximum tolerated dose (MTD) was not reached. The SMC recommended to proceed with enrollment of Group 3 at the maximum dose of 30 mg/kg PGDM1400 and 30 mg/kg PGT121. Enrollment into Group 3 (HIV-infected viremic) began in November 2018 and it is estimated to be completed at the end of June 2019.

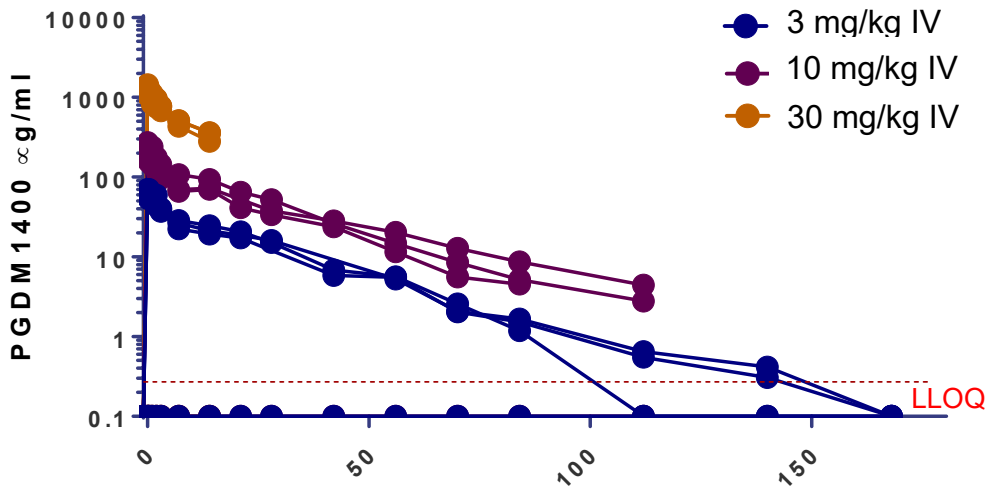

Figure 4-8 PGDM1400 binding antibody concentrations in Group 1A (HIV uninfected, 3 mg/kg), Group 1B (HIV uninfected, 10 mg/kg), and Group 1C (HIV uninfected, 30 mg/kg). LLOQ indicates lower limit of quantitation.

4.6.1.3 IAVI T003

IAVI T003 is a phase 1/2a, open-label clinical trial of the safety, tolerability, pharmacokinetics, and antiviral activity of PGT121, VRC07-523LS and PGDM1400 in HIV-uninfected and HIV-infected adults. The study design is shown below in Table 4-7.

Table 4-7: 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: ART: Antiretroviral Therapy; ATI: Analytical Treatment Interruption (starting on Day 2 after participants complete their full course of ART for Day1 an after first IV infusion on Day 0); IV: intravenous; N/A: not applicable.

As of March 2019, PGT121 has been administered in combination with VRC07-523LS to 3 participants in the IAVI T003 trial. There have been no Grade 3 or higher local or systemic reactions, or related adverse events. One participant reported transient Grade 1 light-headedness on the same day as study product administration.

4.6.2 Clinical studies of VRC07-523LS

4.6.2.1 VRC 605

VRC 605 is a phase 1, open-label, dose-escalation study of VRC07-523LS (NCT03015181) in healthy, HIV-uninfected adults to evaluate the safety and pharmacokinetics of 1 to 3 administrations of the antibody. The study is fully enrolled and study product administration is complete. The doses evaluated were a single administration of 1 mg/kg and 5 mg/kg IV and SC, 20 mg/kg and 40 mg/kg IV, and 3 administrations (q 12 weeks) of 5 mg/kg SC and 20 mg/kg IV VRC07-523LS (Table 4-8).

Study objectives included evaluating the safety and tolerability of the study regimen and the pharmacokinetics of each dose level, determining the presence or absence of detectable ADA to VRC07-523LS, and evaluating for evidence of functional activity of VRC07-523LS.

Table 4-8 VRC 605 study schema

Group	Participants	Administration Schedule		
		Day 0	Week 12	Week 24
1	3	1 mg/kg IV		
2	3	5 mg/kg IV		
3	3	5 mg/kg SC		
4	3	20 mg/kg IV		
5	3	40 mg/kg IV		
6	5	5 mg/kg SC	5 mg/kg SC	5 mg/kg SC
7	5	20 mg/kg IV	20 mg/kg IV	20 mg/kg IV
Total	25			

IV = intravenous infusion
SC = subcutaneous injection

In VRC 605, a total of 41 administrations of VRC07-523LS occurred during the study. VRC07-523LS was safe and well tolerated, with no SAEs or dose-limiting toxicities. All reported local and systemic reactogenicity was mild to moderate in severity. Six AEs were determined to be possibly related to VRC07-523LS administration. One participant in group 5 exhibited grade 1 dizziness on the day of infusion, and 1 in group 7 reported grade 1 abdominal pain the day after infusion. Two volunteers (one each in groups 5 and 7) displayed either grade 1 or grade 2 infusion reactions following each administration, with symptoms typical of those observed following receipt of monoclonal antibodies: fever, chills, myalgia, nausea, and headache. Sera collected from the group 7 participant after each infusion showed an elevation of serum cytokines including Tumor necrosis factor alpha (TNF-a), Interleukin (IL)-6, and IL-13. Importantly, the levels of histamine, tryptase, Interferon gamma (IFN-g), sIL-2R, IL-1b, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, and IL-17 remained within normal levels, and the reaction grade decreased in this participant from grade 2 during the first two infusions to grade 1 during the final infusion. There were no symptoms of hypotension, urticaria, bronchospasm, or other symptoms of severe infusion reactions. Both volunteers were treated symptomatically with acetaminophen and ibuprofen. All symptoms resolved within 12 hours without increased monitoring required.

Interim PK based on preliminary data suggest the average compartmental half-life of VRC07-523LS is 33 ±10 days, with an estimated 28-day trough after one 5 mg/kg SC injection calculated at 27 (SD = 12) mcg/mL.

Figure 4-9 displays interim and confidential VRC07-523LS PK data from VRC 605.

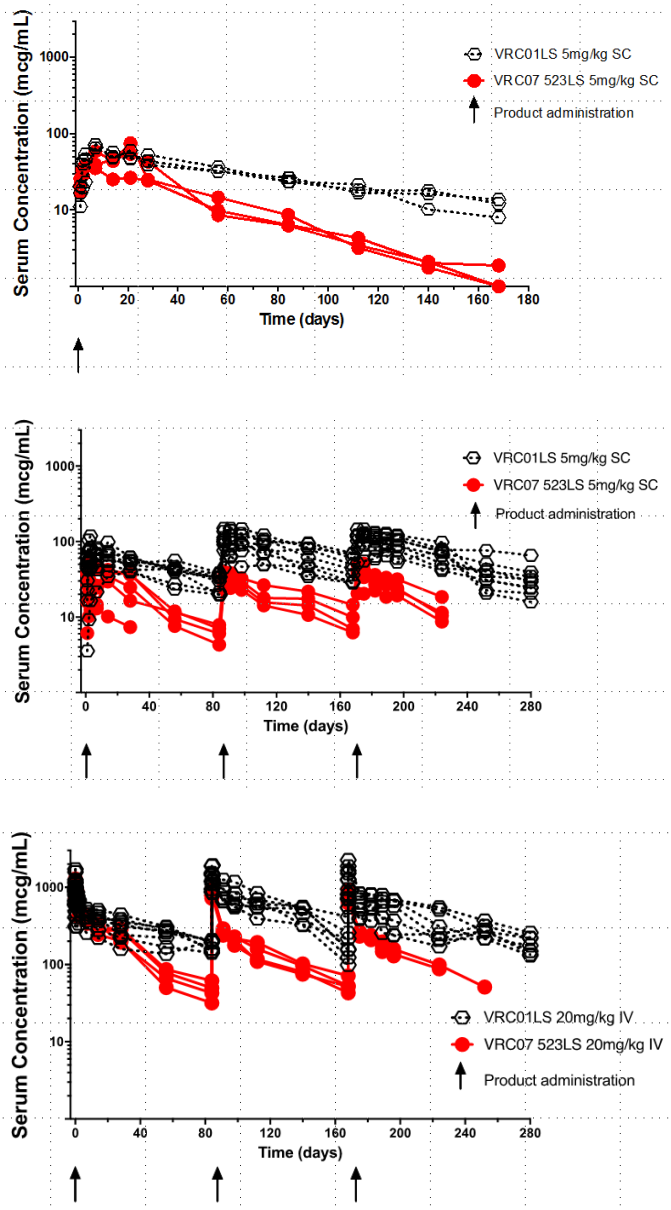

Figure 4-9 (Top) Serum concentration of VRC01LS (from VRC 606) and of VRC07-523LS (from VRC 605) after a single SC injection of 5 mg/kg for each product. (Middle) Serum concentrations of VRC01 LS (from VRC 606) and of VRC07-523LS (from VRC 605) after 3 SC injections of 5 mg/kg for each product. (Bottom) Serum concentrations of VRC07-523LS (from VRC 605) after 3 IV infusions of 20 mg/kg. (Confidential–interim and preliminary; VRC study team personal communication)

4.6.2.2 HVTN 127/HPTN 087

HVTN 127/HPTN 087 (NCT03387150) is a randomized phase 1 clinical trial evaluating the safety and serum concentrations of VRC07-523LS administered in multiple doses via different routes to healthy, HIV-uninfected adults (Table 4-9).

Table 4-9 HVTN 127/HPTN 087 (Version 2.0) study schema

Group	N	Route	Dose	VRC07-523LS administration schedule				
				W0	W16	W32	W48	W64
1	20	IV	2.5 mg/kg	X	X	X	X	X
2	20	IV	5 mg/kg	X	X	X	X	X
3	20	IV	20 mg/kg	X	X	X	X	X
4	20	SC	2.5 mg/kg	X	X	X	X	X
5	20	SC	5 mg/kg	X	X	X	X	X
6	20	IM	2.5 mg/kg	X	X	X	X	X
	4		Placebo	X	X	X	X	X
Total	**124**							

IV = intravenous infusion
SC = subcutaneous injection
IM = intramuscular injection

Between February and October 2018, HVTN 127/HPTN 087 enrolled 124 healthy, HIV-uninfected adult participants to receive multiple administrations of VRC07-523LS via IV, SC, or IM routes (IM added in protocol version 2.0; 4 IM participants receive placebo). The primary objectives of the study are to assess safety and tolerability of repeated IV, SC, or IM administrations of VRC07-523LS and to characterize serum concentration over time for different doses, schedules, and routes of administration. Additional objectives include building a population PK model of VRC07-523LS and determining whether ADAs emerge in response to repeated administrations of the antibody.

One Grade 3 elevated alanine aminotransferase (ALT) deemed related to VRC07-523LS has been reported; the remaining AEs deemed related have been grade 1 (mild) or grade 2 (moderate). No related SAEs have been reported as of May 2019. Four mAb reactions have been reported in three participants, including: (1) grade 1 generalized pruritus in a participant in Group 2 (5 mg/kg IV) after her first infusion; (2) grade 1 generalized pruritus in a participant in Group 5 (5 mg/kg SC) after the second series of SC injections; and (3) two infusion related reactions in a participant in Group 3 (20 mg/kg IV)- the first occurred after his first infusion and was grade 2 and characterized by chills, myalgia, arthralgia, malaise/fatigue, nausea and headache and the second occurred after his second infusion and was grade 1 and characterized by malaise/fatigue, chills and myalgia.

4.6.2.3 HVTN 128

HVTN 128 is a randomized, phase 1 clinical trial that evaluates the safety, tolerability and pharmacokinetics of VRC07-523LS in the sera and mucosae of healthy, HIV-uninfected adults (Table 4-10).

Table 4-10 HVTN 128 (Version 1.0) study schema

Group	N*	Route	VRC07-523LS Dose	Product administration schedule		
				D0	D112	D224
				W0	W16	W32
1	12	IV	10 mg/kg	X	X	X
2	12	IV	30 mg/kg	X	X	X
Total	24					

IV = intravenous infusion
N* = number of participants receiving at least one product infusion

As of May 2019, ten IV infusions of VRC07-523LS have been administered in the HVTN 128 trial. Four mAb reactions after first product administration have been reported in four participants including: (1) grade 1 facial flushing in a participant who enrolled into Group 2 (30 mg/kg IV); (2) grade 2 generalized pruritus in a participant in Group 2 (30 mg/kg IV); (3) grade 1 oropharyngeal itching in a participant who was randomized to Group 1 (10 mg/kg IV); and (4) grade 1 mAb reaction characterized by mild tachycardia, nausea, chills and headache in a participant enrolled in Group 1 (10 mg/kg IV). No other AEs deemed related or related SAEs to VRC07-523LS have been reported.

4.6.2.4 HVTN 130/HPTN 089

HVTN 130/HPTN 089 is a randomized, phase 1 clinical trial that will evaluate the safety, tolerability and serum concentrations of PGT121, PGDM1400, 10-1074 and VRC07-523LS when given sequentially in single and multiple doses via IV administration to healthy, HIV-uninfected adults (Table 4-11). This study opened in July 2019.

Table 4-11 HVTN 130/HPTN 089 (Version 1.0) study schema

Study arm	N	Dose	Route	M0	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*	9	20+20+20 mg/kg	IV	PGDM1400 PGT121 VRC07-523LS	PGDM1400 PGT121 VRC07-523LS
Total	27				

IV = intravenous infusion. The mAbs are infused sequentially in the order shown.
* Opening enrollment in Group 4 follows review of safety data for all participants in Groups 1-3.

4.7 Potential risks of study products and administration

General Risks of mAbs:

Overall, the side effects of mAbs (including for indications other than HIV) are mild and can include fever, flushing, chills, rigors, nausea, vomiting, diarrhea, pain, pruritus, rash, urticaria, angioedema, headache, dizziness, shortness of breath, bronchospasm, tachycardia, hypotension, hypertension, and chest pain. There can also be a risk of infection from mAbs targeting human cytokines or human cell antigens, but since PGT121.414.LS and VRC07-523LS target viral antigens rather than human cell surface antigens and are human mAbs, serious infusion reactions are expected to be rare (77).

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 used in the treatment of rheumatological disorders and cancer. 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. These mAb-related events typically occur within the first 24 hours of administration. 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. Reactions related to the rate of infusion have been described for several FDA-licensed mAbs. Cytokine release syndrome can be effectively managed by temporarily holding the administration, administering anti-histamines, and restarting the IV infusion at a slower rate (78).

Most infusion-related events occur within the first 24 hours after beginning administration. Delayed allergic reactions to a mAb may include a serum sickness type of reaction, characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days to a few weeks after the exposure to the mAb and are noted to be more common with chimeric types of mAb (77, 79).

Other potential side effects of mAbs include thrombocytopenia, autoimmune diseases, cancer, dermatitis, and cardiotoxicity (77).

Risks of the study product(s):

Experience is accruing with each of the PGT121 and VRC07523-LS mAbs alone and in combinations mentioned above (Section 4.6) but HVTN 136/HPTN 092 evaluating PGT121.414.LS alone and in combination with VRC07-523LS will be a first-in-human for the LS-modified form of PGT121. Human experience with PGT121 is limited to the IAVI T001, T002, and T003 clinical trials.

As of March 2019, the IAVI T001, T002, and T003 trials accrual is ongoing, and there have been no related SAEs. There has been 1 unrelated SAE (hospital admission for orthopedic surgery and IV antibacterial treatment for pre-patelar bursitis) in T001. To date, there have been no study safety pauses for AEs and product administrations have been generally well tolerated.

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 (72). SC administration of VRC01 was generally well-tolerated and associated with mild to moderate local pain and/or tenderness, but there was no difference in the frequency or severity between VRC01 recipients and placebo recipients. Erythema and/or induration at the SC injection sites were generally less than 25 cm^2 whether VRC01 or placebo was injected (72). No hypersensitivity reactions or cytokine release syndrome symptoms were reported in HVTN 104 (72).

The ongoing efficacy trials HVTN 704/HPTN 085 and HVTN 703/HPTN 081 have accumulated significant additional VRC01 clinical experience. More than 20,000 infusions of 10 mg/kg and 30 mg/kg VRC01 have been given to more than 5000 HIV-uninfected adults in both trials. However, as these trials remain blinded, they do not yet contribute to the unblinded VRC01 safety profile.

Early-phase human experience with administration of VRC07-523LS has been reassuring in the VRC605 and HVTN127/ HPTN 087 trials (see Section 4.6.2). The majority of participants have reported no local or systemic Solicited AEs and no Unsolicited AEs. Severe reactions associated with mAb administration, such as

acute anaphylaxis, serum sickness, anti-drug antibodies, and increased risk of infections have not been observed to date in trials of VRC01-class mAbs.

Risk of HIV seroreactivity: 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 of blood drawing: Blood drawing may cause pain and bruising and may infrequently cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site and rarely, infection, phlebitis, or blood clot. Risk will be minimized by using sterile technique and universal precautions. Blood drawing may also cause anemia.

Risks of IV infusion: The placement of an intravenous catheter can allow for the development of bacteremia because of the contact between the catheter and unsterile skin during insertion. Risk of infection from IV infusion will be minimized through careful decontamination of local skin prior to catheter placement and through the use of infection control practices during infusion. The risk of product contamination will be minimized by the use of aseptic technique in the pharmacy and universal precautions during product administration.

Risks of SC infusion: SC administration can result in pain, nodule formation, local edema, and possible infection. The risk of infection from SC administration will be minimized through skin decontamination of the skin prior to needle insertion. The risk of product contamination will be the same as for IV administration and will be minimized through the use of aseptic technique during product preparation and administration.

5 Objectives and endpoints

5.1 Primary objectives and endpoints

Primary objective 1

- To evaluate the safety and tolerability of the PGT121.414.LS monoclonal antibody (mAb) when administered alone via intravenous (IV) or subcutaneous (SC) infusion (Part A) and of PGT121.414.LS and VRC07-523LS administered consecutively via IV or SC routes at and after each product administration visit (Part B)

Primary endpoints 1

- Local and systemic solicited AEs, laboratory measures of safety, and 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 pharmacokinetic (PK) properties of PGT121.414.LS after a single administration (Part A) and of PGT121.414.LS and VRC07-523LS after consecutive administration of the pair of mAbs at and after each of 3 quarterly visits (Part B)

Primary endpoint 2

- Serum concentrations of PGT121.414.LS and VRC07-523LS at prespecified timepoints among participants who received all scheduled product administrations

Primary objective 3

- To evaluate the individual mAb-specific serum neutralizing activity of PGT121.414.LS after a single administration (Part A) and of PGT121.414.LS and VRC07-523LS after consecutive administration of the pair of mAbs at and after each of 3 quarterly visits (Part B).

Primary endpoint 3

- Magnitude of serum neutralizing activity measured with mAb-specific Env-pseudotyped viruses in TZM-bl cells from samples obtained 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 PGT121.414.LS and VRC07-523LS with corresponding virus neutralization titers in serum

Secondary endpoints 1

- Serum concentrations of PGT121.414.LS and VRC07-523LS at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

- 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 2

- To determine whether the mAbs maintain their expected combined magnitude and breadth of serum neutralizing activity as predicted by the known magnitude and breadth of neutralization of the corresponding mAb combinations as non-infused clinical products in vitro

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, and for the clinical product assayed at the same time.

Secondary objective 3

- To determine whether ADA are present and whether there is a correlation between PGT121.414.LS and VRC07-523LS concentrations and ADA titers in serum samples

Secondary endpoint 3

- Serum PGT121.414.LS and VRC07-523LS concentrations and ADA titers 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 PGT121.414.LS and VRC07-523LS

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) may be performed for activities that PGT121.414.LS and VRC07-523LS are shown to exhibit in vitro

Exploratory objective 3

To develop predictive population PK models and to assess PK, drug-drug interaction, and neutralization drug-drug interaction among PGT121.414.LS and VRC07-523LS

Exploratory objective 4

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 5

To conduct analyses related to furthering the understanding of HIV, monoclonal antibodies, immunology, vaccines, and clinical trial conduct

6 Statistical considerations

6.1 Accrual and sample size calculations

Recruitment will target enrolling 32 healthy, HIV-uninfected adult participants. In Part A of the study, PGT121.414.LS will be administered as a single IV infusion at 3, 10, or 30 mg/kg (Groups 1-3) or a 5 mg/kg SC dose (Group 4) with n=3 participants per group. Groups 1 and 2 will enroll sequentially, and Groups 3 and 4 will be randomized in a 1:1 ratio. In Part B of the study, participants will receive 3 doses of PGT121.414.LS + VRC07-523LS at 20 mg/kg IV each per dose (Group 5) or 5 mg/kg SC each per dose (Group 6). Groups 5 and 6 will be randomized in a 1:1 ratio with n=10 participants per group. All groups 1-6 are open-label. To ensure that both persons assigned male sex at birth and persons assigned female sex at birth will be adequately represented, the trial will enroll at least approximately 40% of each. In Part A, each of Groups 1-4 will enroll at least one person of each sex assigned at birth. In Part B, each Groups 5-6 will enroll at least four people of each sex assigned at birth.

Since enrollment is concurrent with receiving the first product administration, all participants will provide some safety data. However, it is possible that data may be missing for various reasons, such as participants terminating from the study early, problems in shipping specimens, or high assay background. For this reason, the sample size calculations account for 20% of enrolled participants having missing data for the primary lab endpoint at a given timepoint. As a reference, immunogenicity data from 17 phase 1 and 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 15% of mAb concentration data were missing at the primary timepoints.

6.1.1 Sample size calculations for safety

This study is primarily descriptive. The goal of the safety evaluation for this study 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 above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. Specifically, for each treatment group of size n = 3 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 53.6% or more; and there is a 90% or more chance of observing no events if the true rate is 3.4% or less. For IV infusion Groups 1-3 combined with n=9 in Part A, there is a 90% chance or more of observing at least 1 event if the true rate is 22.6% or more; and there is a 90% chance or more of observing no events if the true rate is 1.2% or less. For Groups 1-4 combined with n=12 in Part A, there is 90% chance or more of observing at least 1 event if the true rate is 17.5% or more; and there is a 90% chance or more of observing no events if the true rate is 0.9% or less. For each group of size n=10 in Part B, there is 90% or more chance of observing at least 1 event if the true rate of such an

event is 20.6% or more; and there is 90% or more chance of observing no events if the true rate is 1.1% or less. For Groups 5 and 6 combined with n=20 in Part B, there is 90% or more chance of observing at least 1 event if the true rate of such an event is 11.0% or more; and there is 90% or more chance of observing no events if the true rate is 0.5% or less. As a reference, 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 3, 9, 12, and 20 for different true event rates

Group size	True event rate (%)	Pr(0/n_1)	Pr(1+/n_1)	Pr(2+/n_1)
3	1	0.97	0.03	<0.01
	4	0.88	0.12	<0.01
	10	0.73	0.27	0.03
	20	0.51	0.49	0.10
	30	0.34	0.66	0.22
9	1	0.91	0.09	<0.01
	4	0.69	0.31	0.05
	10	0.39	0.61	0.23
	20	0.13	0.87	0.56
	30	0.04	0.96	0.80
12	1	0.89	0.11	0.01
	4	0.61	0.39	0.08
	10	0.28	0.72	0.34
	20	0.07	0.93	0.73
	30	<0.01	>0.99	0.91
20	1	0.72	0.28	0.04
	4	0.27	0.73	0.37
	10	0.03	0.97	0.84
	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 VRC07-523LS and PGT121.414.LS at several timepoints (ie, pharmacokinetics) following IV or SC administration of these mAbs. This objective is descriptive in nature 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 displays two-sided 95% confidence intervals (CIs) for the mean mAb concentration for several values of the observed average mAb concentration. The construction of these confidence intervals assumed sample sizes of n = 8 per arm, reflecting a missingness rate of 20%, compared to a planned treatment group size of 10 participants. 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 a standard deviation of 0.5 for their log-transformed values, a two-sided 95% confidence interval for the true mean mAb concentration level is (6.6, 15.2) (in mcg/mL) with an effective sample size of 8 participants. Of note, a SD of less than 1.0 was generally observed in the log-transformed serum concentrations of VRC01 at various timepoints post IV infusions or SC infusions of VRC01 in HVTN104 (71).

Table 6-2 Two-sided 95% confidence intervals based on observing a particular average $\log_e$ mAb concentration in Part B participants, taking 15% attrition into consideration (n = 8/arm)

Observed average $\log_e$-mAb concentration ($\log_e$ mcg/mL)	SD of $\log_e$-mAb concentration ($\log_e$ mcg/mL)	95% confidence interval (mcg/mL)
$\log_e$(1)	0.5	(0.7, 1.5)
$\log_e$(10)		(6.6, 15.2)
$\log_e$(50)		(32.9, 75.9)
$\log_e$(100)		(65.8, 151.9)
$\log_e$(500)		(329.2, 759.5)
$\log_e$(1000)		(658.4, 1518.9)
$\log_e$(1)	1.0	(0.4, 2.3)
$\log_e$(10)		(4.3, 23.1)
$\log_e$(50)		(21.7, 115.4)
$\log_e$(100)		(43.3, 230.7)
$\log_e$(500)		(216.7, 1153.6)
$\log_e$(1000)		(433.4, 2307.2)

6.1.3 Sample size calculations for serum neutralization activity

Primary objective 3 of this study is to evaluate serum neutralization titers of VRC07-523LS and PGT121.414.LS, against Env-pseudotyped viruses specific to each mAb at several timepoints following IV or SC administrations. This objective is also descriptive in nature, and will be accomplished by estimating, within each treatment group, the mean serum neutralization titers of each mAb against the specific virus. 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 displays two-sided 95% confidence intervals for the mean neutralization titer for several values of the observed average infectious dose (ID)50 or ID80 neutralization titer. The construction of these confidence intervals assumed sample sizes of n = 8 per group, reflecting an attrition rate of 20% compared to the planned treatment group size of 10 participants,

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 a standard deviation of 0.5 for their log-transformed values, a two-sided 95% confidence interval for the true mean neutralization titer is (32.9, 75.9) with an effective sample size of 8 participants. Of note, based on neutralization data against a global panel of 11 pseudoviruses in 6 participants in HVTN104, an SD of approximately 1.0 was observed in the $\log_e$-transformed ID50 titers at various timepoints post IV infusions of VRC01 (71).

Table 6-3 Two-sided 95% confidence intervals based on observing a particular average $\log_e$-neutralization titer in participants in any of the active arms, taking 15% attrition into consideration (n = 5 or 7)

Observed average $\log_e$ neutralization titer	SD of $\log_e$ neutralization titer	95% confidence interval
$\log_e(10)$	0.5	(6.6, 15.2)
$\log_e(50)$		(32.9, 75.9)
$\log_e(100)$		(65.8, 151.9)
$\log_e(500)$		(329.2, 759.5)
$\log_e(1000)$		(658.4, 1518.9)
$\log_e(10)$	1.0	(4.3, 23.1)
$\log_e(50)$		(21.7, 115.4)
$\log_e(100)$		(43.3, 230.7)
$\log_e(500)$		(216.7, 1153.6)
$\log_e(1000)$		(433.4, 2307.2)

6.2 Randomization

There will be no randomization for Groups 1 and 2 as they will be enrolled sequentially for dose escalation. Contingent on safety data from Groups 1 and 2, Groups 3 and 4 will be randomized and enrolled simultaneously. Contingent on data from Groups 1-4, Groups 5 and 6 will be randomized in blocks to ensure balance across groups for simultaneous enrollment. 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 group assignments. Laboratory program 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

All safety data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many study product administrations 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 neutralizing activity data are per-protocol (PP) in that only individuals who receive the expected mAb combination at the expect 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 non-compartmental PK and population PK analyses (eg, NONMEM). 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 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, serum mAb concentrations, neutralization, 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 will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom reported more than once, each participant's Solicited AEs will be counted once under the maximum severity for all infusion visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration or erythema, and of 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 will be summarized using 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 study product 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 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version specified in Study Specific Procedures [SSP]/Statistical Analysis Plan [SAP]) will be tabulated by treatment arm for each poststudy 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 Serum concentration and PK analysis

6.4.4.1 Primary analyses of serum concentrations

The primary analysis of serum concentration and pharmacokinetics of the evaluated mAbs (Primary Objective 2) will be restricted to participants who received all scheduled administrations per-protocol. Serum concentrations that appear unreliable, or from specimens collected outside of the visit window, or from HIV-infected participants postinfection may be excluded. The primary analysis of serum concentration will be descriptive and will be performed separately for each mAb. A non-compartmental pharmacokinetic analysis will be performed on the concentration data. Pharmacokinetic parameters may include, but are not limited to: area-under-the-curve (AUC), maximum concentration (C_{max}), time to C_{max} (T_{max}), clearance (CL), volume of distribution (Vd), terminal elimination rate constant (λz) and the terminal half-life ($T_{1/2}$). Data will be summarized by group and overall for CL, Vd, and $T_{1/2}$. Individual-level two-compartmental models may also be considered. Graphical displays of the data (eg, boxplots, scatterplots, histograms, spaghetti plots) will be generated to visually explore distributional properties of the data as well as potential pairwise associations. These summary statistics and graphical displays may be produced for each treatment arm and each timepoint separately.

6.4.4.2 Exploratory analyses of serum concentrations via population PK models

Population PK (popPK) models of each mAb may be developed to describe the overall kinetics of serum concentration and the variation of the kinetics between and within healthy, HIV-uninfected adults based on non-linear mixed effects models. Data from all enrolled participants will be analyzed regardless of how many administrations and how much mAb dose they received (MITT analysis). Serum concentration data from specimens collected outside of the visit window may be included in popPK 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 infection is unknown, any serum level data from blood draws 4 weeks prior to an infected participant's last seronegative sample and thereafter may be excluded. All data from HIV-infected participants who have no seronegative samples post enrollment may be excluded from the analysis.

The popPK models will describe the pharmacokinetics of each mAb at the individual level using a compartmental approach. Based on a previous population PK analysis of the serum concentrations of VRC01 (71), we anticipate that a two-compartmental model can characterize the kinetics of the serum concentrations of the mAbs. In the event that modeling assumptions appear violated, we will consider other compartmental models. Comparisons of PK parameters across treatment groups will be performed using either likelihood ratio or Wald tests. Estimates of metrics of interest as a function of the PK parameters, including half-life and steady state concentration will be derived from these analyses.

6.4.5 Analysis of neutralization activity and correlation with serum concentrations

6.4.5.1 Primary and secondary analyses of serum neutralization titers

The primary analysis of serum neutralization titers against each mAb-specific virus will be restricted to participants who received all scheduled administrations per-protocol. Serum neutralization titers that appear unreliable, or from specimens collected outside of the visit window, or from HIV-infected participants post infection may be excluded. This analysis of serum neutralization titers will be descriptive and will be performed separately for each mAb. To address Secondary objective 3, at each specified timepoint, the area-under-the-magnitude-breadth curve (AUC-MB) to a panel of viral isolates (80) will be computed for each participant with evaluable neutralization ID50 or ID80 data, as described in (81). Magnitude–Breadth (M-B) curves may 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. Two choices are to compare the M-B curves among arms, as follows: a non-parametric Wilcoxon rank sum test on the subject-specific area-under-the M-B curve (AUC M-B) or a Kolmogorov-Smirnov type test on the 2 group-average M-B curves. Simulations can be used to obtain two-sided p-values for the latter test. In addition, a weighted-average score-like variable may be constructed to account for the correlations between virus isolates as an integrated magnitude of responses to multiple isolates. Similar group comparison methods described in the first approach may be adopted. 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, data from all enrolled participants will be analyzed regardless of how many administrations and how much mAb dose they received (MITT analysis). Besides descriptive analyses of the correlations, pharmacodynamics (PD) models based on either linear or non-linear mixed effects models may be performed to characterize the correlation between serum concentration (observed or popPK model-predicted) and serum neutralization against each virus or the AUC-MB of serum neutralization against the panel. 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 infection is unknown, any serum concentration data from blood draws 4 weeks prior to an infected participant's last seronegative sample and thereafter may be excluded. All data from HIV-infected participants who have no seronegative samples post enrollment may be excluded from the analysis.

6.4.6 Analysis of ADA and other functional activities in serum

For the analysis of ADA (Secondary objective 4), data from enrolled participants will be used regardless of how many administrations they received (MITT). For Exploratory objectives regarding non-neutralizing anti-viral functionality, data from all enrolled participants will be used. Assay results that are unreliable or from HIV-infected participants post infection will be excluded. Additional exploratory analyses examining the impact of ADA on PK will be described in the SAP.

Univariate and bivariate descriptive analyses of continuous assay data (eg, ADCC) will be performed using mean, median, standard deviation, range, skewness, 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, and 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 the data appear normally distributed, the results of these tests may be compared to those produced by 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 (ie, 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% confidence interval estimates calculated using the score test method (72). Associations between categorical variables will be assessed using Fisher's exact, Barnard's exact test, or Chi-squared tests.

Analysis of longitudinal data may be performed using mixed effects models or generalized estimating equations (GEE). These approaches allow describing

outcome responses over several timepoints while accounting for potential intra-subject correlation.

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 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 (82), Chapters 1, 3, and 6] for elaborate definitions and examples of missing data mechanisms and Ibrahim et al (83) 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' (84) linear mixed effects models to accommodate censoring. In addition, exploratory analyses of repeated functional measurements may be done using weighted GEE (85) 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.

6.4.7 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 safety or laboratory endpoint assessments.

6.4.7.1 Safety

During the course of the trial, 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 136/HPTN 092 PSRT.

7 Selection and withdrawal of participants

Participants will be healthy, HIV-uninfected (seronegative) adults who 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.

Investigators should always use good clinical judgment in considering a volunteer's overall fitness for trial participation. Some volunteers may not be appropriate for enrollment even if they meet all inclusion/exclusion criteria. Medical, psychiatric, occupational, or other conditions may make evaluation of safety and/or other endpoints difficult, and some volunteers may be poor candidates for retention.

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 to 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**: 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 infection risks** and amenable to HIV risk reduction counseling.

9. Assessed by the clinic staff as being at **"low risk" for HIV infection** and committed to maintaining behavior consistent with low risk of HIV exposure through the last required protocol clinic visit (see Appendix Q).

Laboratory Inclusion Values

Hemogram/Complete Blood Count

10. **Hemoglobin** ≥ 11.0 g/dL for participants who were assigned female sex at birth, ≥13.0 g/dL for participants who were assigned male sex at birth. For transgender participants who have been on feminizing hormone therapy for more than 6 consecutive months, determine hemoglobin eligibility based on the gender with which they identify (ie, a transgender female who has been on hormone therapy for more than 6 consecutive months should be assessed for eligibility using the hemoglobin parameters for persons assigned female sex at birth).

11. **White blood cell 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**: **ALT** < 1.25 times the institutional upper limit of normal; **creatinine** ≤ institutional upper limit of normal

Virology

15. **Negative HIV-1 and -2 blood test**: US volunteers must have a negative FDA-approved enzyme immunoassay (EIA) or chemiluminescent microparticle immunoassay (CMIA).

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

17. **Negative anti-Hepatitis C virus antibodies (anti-HCV)**, or negative HCV polymerase chain reaction (PCR) if the anti-HCV is positive

Urine

18. **Negative or trace urine protein**

Reproductive Status

19. **Volunteers who were assigned female sex at birth**: negative serum or urine beta human chorionic gonadotropin (β-HCG) pregnancy test performed prior to study product administration on the day of initial study product administration. Persons who are NOT of reproductive potential due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

20. **Reproductive status**: A volunteer who was assigned female sex at birth 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 clinic visit. Effective contraception is defined as using the following methods:
        - Condoms (male or female) 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 136/HPTN 092 PSRT
        - Successful vasectomy in any partner assigned male sex at birth (considered successful if a volunteer reports that a male 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 reproductive potential, such as having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy;

    - Or be sexually abstinent.

21. **Volunteers who were assigned female sex at birth must also agree not to seek pregnancy through alternative methods**, such as artificial insemination or in vitro fertilization until after the last required protocol clinic visit

7.2 Exclusion criteria

General

1. **Weight > 115 kg**

2. **Blood products** received within 120 days before first study product administration, unless eligibility for earlier enrollment is determined by the HVTN 136/HPTN 092 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 antibody testing during the planned duration of the study

5. **Pregnant or breastfeeding**

Vaccines and other Injections

6. **HIV vaccine(s)** received in a prior HIV vaccine trial. For volunteers who have received control/placebo in an HIV vaccine trial, the HVTN 136/HPTN 092 PSRT will determine eligibility on a case-by-case basis.

7. **Previous receipt of humanized or human mAbs,** whether licensed or investigational; the HVTN 136/HPTN 092 PSRT will determine eligibility on a case-by-case basis.

8. **Previous receipt of monoclonal antibodies VRC01, VRC01LS, VRC07-523LS, or PGT121**

Immune System

9. **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.)

10. **Serious adverse reactions** to VRC07-523LS or PGT121.414.LS formulation components (acetate, sucrose, polysorbate 80, histidine, and sorbitol; see Section 8.2), including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain

11. **Immunoglobulin** received within 90 days before first study product administration, unless eligibility for earlier enrollment is determined by the HVTN 136/HPTN 092 PSRT (for mAb see criterion 7 above)

12. **Autoimmune disease** (Not excluded from participation: Participant with mild, stable and uncomplicated autoimmune disease that does not require immunosuppressive medication and that, in the judgment of the site investigator,

is likely not subject to exacerbation and likely not to complicate Solicited and Unsolicited AE assessments)

13. **Immunodeficiency**

Clinically significant medical conditions

14. **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:

    - 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 or subcutaneous 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.

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

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

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

18. **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).

19. 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 either of the following:
  - Greater than 1 exacerbation of symptoms treated with oral/parenteral corticosteroids;
  - Needed emergency care, urgent care, hospitalization, or intubation for asthma.

20. **Diabetes mellitus** type 1 or type 2 (Not excluded: type 2 cases controlled with diet alone or a history of isolated gestational diabetes.)

21. **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 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.

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

23. **Malignancy** (Not excluded from participation: 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)

24. **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.

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

26. History of generalized urticaria, angioedema, or anaphylaxis.

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 11.4.

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

Under certain circumstances, a participant's scheduled study product administration will be delayed. Refer to the HVTN 136/HPTN 092 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])

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

- Intercurrent illness that is assessed by the site principal investigator (or designee) to require delaying product administration. The investigator may consult the HVTN 136/HPTN 092 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 breast-feeding and study product administration can be performed within an appropriate visit window, study product administration may resume with unanimous consent of the HVTN 136/HPTN 092 PSRT.

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 administration cannot be given. The participant should be asked to continue study visits. For Groups 5 and 6 in Part B, the participant should resume the study product administration schedule with the next study product administration unless there are circumstances that require further delay or permanent discontinuation of study product administration (see Sections 7.3.3 and 7.3.4).

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:

- Co-enrollment 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 136/HPTN 092 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 infection
  - 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 136/HPTN 092 PSRT may allow continuation of study product.
  - 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 136/HPTN 092 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 infection 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 136/HPTN 092 SSP).

Participants diagnosed with HIV infection 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 preparation and administration

CRS pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. The protocol schema is shown in Table 1-1. See the IB for further information about study products.

8.1 Study product regimen

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

Group 1

Treatment 1 (T1): PGT121.414.LS 3 mg/kg to be administered IV at Month 0

Group 2

Treatment 2 (T2): PGT121.414.LS 10 mg/kg to be administered IV at Month 0

Group 3

Treatment 3 (T3): PGT121.414.LS 30 mg/kg to be administered IV at Month 0

Group 4

Treatment 4 (T4): PGT121.414.LS 5 mg/kg to be administered via SC infusion at Month 0

Group 5

Treatment 5 (T5): PGT121.414.LS 20 mg/kg AND VRC07-523LS 20 mg/kg to be administered IV sequentially in this order at Month 0, Month 4, and Month 8

Group 6

Treatment 6 (T6): PGT121.414.LS 5 mg/kg AND VRC07-523LS 5 mg/kg to be administered via SC infusion sequentially in this order at Month 0, Month 4, and Month 8

8.2 Study product formulation

8.2.1 PGT121.414.LS [Labeled as PGT121.414.LS Drug Product (VRC-HIVMAB0107-00-AB)]

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, 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).

8.2.2 VRC07-523LS Labeled as VRC07-523LS HIV MAb (VRC-HIVMAB075-00-AB))]

VRC07-523LS will be supplied as 10 mL single-use glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL single-use glass vials with a 2.25 mL ± 0.1 mL fill volume, at a concentration of 100 ± 10 mg/mL. Each vial contains a clear, colorless to yellow isotonic, preservative free, sterile solution essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of histidine, sodium chloride, sucrose, and sorbitol at pH 6.8. Vials do not contain a preservative.

VRC07-523LS product label designates the long-term storage as -35°C to -15°C (-31°F to 5°F).

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 upon 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, their institution, and their 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 prepared study product should be discarded in a biohazard container and disposed of in accordance with institutional or pharmacy policy.

8.3.1 PGT121.414.LS

8.3.1.1 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, avoid 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 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.

8.3.1.2 PGT121.414.LS intravenous infusion preparation

1. Calculate the total dose (mg) of PGT121.414.LS required based on the participant's weight (in kg) and treatment dose of 3 mg/kg, 10 mg/kg, 20 mg/kg, or 30 mg/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 Sodium Chloride for Injection, 0.9% 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 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.

8.3.1.3 PGT121.414.LS subcutaneous infusion preparation

1. Calculate the total (mg) of PGT121.414.LS required based on the participant's weight (in kg) and the treatment group of 5 mg/kg. Remove the minimum number of thawed PGT121.414.LS vials from storage.

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

3. Using aseptic technique, withdraw the calculated volume of PGT121.414.LS from the vial(s) into the final container using a 5 micron filter needle (see HVTN 136/HPTN 092 SSP for needle/filter specifications and details). A new filter needle must be used for each container. Discard the filter needle prior to dispensing. **Record this as the study product preparation time**.

4. The prepared PGT121.414.LS product may be stored at 2°C to 8°C 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 VRC07-523LS

VRC07-523LS is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing.

8.3.2.1 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, avoid foaming. DO NOT SHAKE THE VIALS. **If particles are observed, return the vials to 2°C to 8°C storage.** If the particles re-dissolve within the maximum storage times described in #4 below,

they may be used for product preparation. **If particles continue to be observed, do not use the vials.**

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

8.3.2.2 VRC07-523LS intravenous infusion preparation

1. Calculate the total dose (mg) of VRC07-523LS required based on the participant's weight (in kg) and treatment dose of 20 mg/kg. Remove the minimum number of thawed particle-free VRC07-523LS vials from storage, as well as an appropriately sized IV container (bag/glass bottle) containing 100 mL of Sodium Chloride for Injection, 0.9% USP, that will also permit the addition of the required calculated volume of VRC07-523LS.

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. Observe vials for particles. If particles are observed, refer to the thawing instructions described above in Section 8.3.2.1.

4. Using aseptic technique, add the calculated volume of VRC07-523 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 VRC07-523LS IV container may be stored at 2°C to 8°C up to 48 hours or at controlled room temperature (maximum 27°C) for a maximum of 4 hours, 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.

8.3.2.3 VRC07-523LS subcutaneous infusion preparation

1. Calculate the total (mg) of VRC07-523LS required based on the participant's weight (in kg) and the treatment group of 5 mg/kg. Remove the minimum number of thawed particle-free VRC07-523LS vials from storage.

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

3. Observe vials for particles. If particles are observed, refer to the thawing instructions described above in Section 8.3.2.1.

4. Using aseptic technique, withdraw the calculated volume of VRC07-523LS from the vial(s) into the final container using a 5 micron filter needle (see HVTN 136/HPTN 092 SSP for needle/filter specifications and details). A new filter needle must be used for each container. Discard the filter needle prior to dispensing. **Record this as the study product preparation time.**

5. The prepared VRC07-523LS syringe(s) may be stored at 2°C to 8°C for up to 24 hours or at room temperature (maximum 30°C) for a maximum of 4 hours, including the administration time. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, prepared product must be equilibrated at room temperature (maximum 30°C) for a minimum of 30 minutes prior to product administration.

8.3.3 Labeling of study products

Label the study product as follows:

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

8.4 Administration

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

In Group 5, two separate IV containers each containing 1 study product will be administered sequentially, PGT121.414.LS first followed by VRC07-523LS.

In Group 6, two separate preparations each containing 1 study product will be administered sequentially, PGT121.414.LS SC infusion first followed by VRC07-523LS SC infusion.

8.4.1 PGT121.414.LS (Intravenous Infusion)

PGT121.414.LS will be administered IV over approximately 30 to 60 minutes. A 1.2 micron in-line filter must be used for IV product administration. Filters must comply with the specifications described in the HVTN 136/ HPTN 092 SSP. Once the in-line filter is added to the tubing, prime the administration set with Sodium Chloride Injection, 0.9% USP. Refer to the HVTN 136/HPTN 092 SSP for further information on IV administration.

8.4.2 PGT121.414.LS (Subcutaneous Infusion)

PGT121.414.LS will be administered via SC infusion at a rate of 15 mL/hr. A suitable needle for SC infusion should be affixed to the prepared product prior to administration.

8.4.3 VRC07-523LS (Intravenous Infusion)

VRC07-523LS will be administered IV over approximately 15 to 60 minutes. A 1.2 micron in-line filter must be used for IV product administration. Filters must comply with the specifications described in the HVTN 136/ HPTN 092 SSP. Once the in-line filter is added to the tubing, prime the administration set with 0.9% Sodium Chloride Injection, USP. Refer to the HVTN 136/HPTN 092 SSP for further information on IV administration.

8.4.4 VR07-523LS (Subcutaneous Infusion)

VRC07-523LS will be administered via subcutaneous infusion at a rate of 15 mL/hr. A needle suitable for SC infusion should be affixed to the prepared product prior to administration.

8.5 Acquisition of study products

PGT121.414.LS is provided by Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, MD, USA).

VRC07-523LS is provided by Dale and Betty Bumpers Vaccine Research Center (VRC), 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, tubing, and 0.9% sodium chloride for injection will be locally sourced by the site. Please refer to the study product considerations section of the HVTN 136/HPTN 092 SSPs 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

For US clinical research sites, all unused study products must be returned to the CRPMC 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 schedules of clinical procedures are shown in Appendix N, Appendix O, Appendix P, and Appendix Q.

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.

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 informed consent forms.

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 subjects 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 knowing 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 site 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 and Title 21 CFR, Part 50, and in ICH E6, 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 level of understandability.

The sample informed consent forms 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

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

An Assessment of Understanding is used to document the participant's understanding of key concepts in this clinical trial. The participant must complete the Assessment of Understanding 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 Assessment of Understanding. The consent process (including the use of the Assessment of Understanding) 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 0. 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 is at low risk for HIV infection (see Appendix R).
- Complete physical examination, including height, weight, 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
  - Hepatitis B surface antigen (HBsAg),
  - Anti-HCV Abs,
  - Syphilis,
  - Complete Blood Count (CBC) with differential,
  - Chemistry panel (alanine aminotransferase [ALT], creatinine),
  - Urine dipstick (urinalyses if indicated; see Section 9.7),
  - Urine or serum pregnancy test (volunteers who were assigned female sex at birth); persons who are not of reproductive potential due to having undergone total hysterectomy with bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing;

- Administration of behavioral risk assessment questionnaire

- Obtaining of 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.

- Discussion of pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and pregnancy status are described in study inclusion criteria. Discussion of pregnancy prevention includes advising a participant who was assigned female sex at birth 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

Enrollment is simultaneous with first study product administration. The study group assignment (all groups) and treatment assignment (Groups 3 and 4 in Part A and Groups 5 and 6 in Part B) will be provided via a Web-based system (see Section 6.2). 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.

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 AEs/intercurrent illnesses; and
- Clinical laboratory tests including:
  - CBC with differential;
  - Chemistry panel (see Section 9.2), and
  - Urine or serum pregnancy test (for participants who were assigned female sex at birth). Persons who are NOT of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;

Following completion of all procedures in the preceding list, and if 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 2 hours. Samples are drawn 1 hour after the last product administration (see Appendix J, Appendix K, Appendix L, and Appendix M).

See the HVTN 136/HPTN 092 SSP for details regarding study product administration visit procedures and subsequent study product observation and

Solicited AE assessment procedures that CRSs must follow. The site will make arrangements to be in contact with the participant during or following the Solicited AE period (as described in Section 9.8 and the HVTN 136/HPTN 092 SSP).

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 capable of becoming pregnant, contraception status assessment (as described in Section 9.2 and 9.6). In persons who are confirmed pregnant, contraception status assessment is not required; and
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation).

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

- Acceptability questionnaire.
- PK Specimen collection (see Appendix J, Appendix K, Appendix L, and Appendix M)

Additional procedures will be performed at scheduled visits as specified in, Appendix N, Appendix O, Appendix P, and Appendix Q:

- Specimen collection (should be completed per Appendix J, Appendix K, Appendix L, and Appendix M).
- HIV infection 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

9.3.1 Managing infusion reactions

Since PGT121.414.LS and VRC07-523LS are human mAbs that target a viral antigen rather than human cell surface antigens, serious mAb reactions are expected to be rare. Nevertheless, participants will be closely monitored in the clinic during study product administration and during a postinfusion observation period. CRS staff are trained to recognize suspected mAb reactions and to provide immediate medical care consistent with the HVTN 136/HPTN 092 SSP.

Medications used to treat mAb reactions may include: acetaminophen, antihistamines, and corticosteroids. CRSs are also equipped with additional emergency medical supplies to provide immediate medical interventions 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 a mAb reaction:

- mAb reaction clinical assessment;
- mAb reaction blood collection.

For detailed management of mAb reactions see the HVTN 136/HPTN 092 SSP

9.4 Follow-up visits

The following procedures are performed at scheduled follow-up visits as specified in Appendix N, Appendix O, Appendix P, and Appendix Q:

- Risk reduction counseling (as described in Section 9.5);
- For participants capable of becoming pregnant, contraception status assessment (as described in Section 9.2 and 9.6). In persons who are pregnant, contraception status assessment is not required;
- Administration of behavioral risk assessment questionnaire;
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has 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 Unsolicited 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);
- HIV infection 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, 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 J, Appendix K, Appendix L, and Appendix M);

- Clinical laboratory tests including:
  - CBC with differential,
  - Chemistry panel (see Section 9.2);
  - Urine dipstick (urinalysis if appropriate; see Section 9.7); and
  - Urine or serum pregnancy test (for participants who were assigned female sex at birth). Persons who are NOT of reproductive 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, pregnancy testing 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 infection.

Potential participants identified as being HIV-infected during screening are not enrolled. Potential and enrolled participants identified as HIV-infected will be referred for medical treatment, counseling, and management of the HIV infection. With respect to enrolled participants who become HIV-infected, 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 is actually infected.

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

9.5.1 Study product-related seroreactivity

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 136/HPTN 092 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.

9.6 Contraception status

Contraception status is assessed and documented at clinic visits indicated in Appendix N, Appendix O, Appendix P, and Appendix Q for a participant who was assigned female sex at birth and who is sexually active in a way that could cause that participant to become pregnant. Prior to enrollment and throughout the study, staff will ask participants to verbally confirm their use of adequate contraceptive methods. A participant who was assigned female sex at birth and is sexually active in a way that could cause that participant to become pregnant 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.

9.7 Urine testing

Dipstick testing may be performed in the clinic or the lab, as long as the required elements (glucose, protein, and hemoglobin) are tested. The examination is performed on urine obtained by clean catch.

If the screening dipstick is transiently abnormal due to non-urinary 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 menstruating but should be performed as soon as possible. If a follow-up dipstick is abnormal due to a participant's menstrual period, document in the comment section of the case report form (CRF) and repeat the dipstick once the participant is no longer menstruating. 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 in the Ab Manual of Operations (MOP) for further details.

9.8 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 Division of AIDS 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.

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. CRS staff and the participant will be in contact during and after the 3-day Solicited AE assessment period, or sooner if indicated. See the HVTN 136/HPTN 092 SSP for further details. In general, a participant who self-reports any poststudy product administration reaction(s) 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 new or unresolved Solicited AEs present at day 3 to resolution.

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, or with an onset after the Solicited AE assessment period (day of study product

administration and 3 full days after), or those meeting SAE/Unsolicited AEs requiring expedited reporting to DAIDS criteria, are recorded on an AE Log.

Table 9-1 Schedule of Solicited AE assessments

Day	Time	Performed by
0[a]	Baseline: before study product administration	CRS clinician
	Early: 25-60 minutes after study product administration	CRS clinician
	Between early assessment and 11:59pm day 0	CRS clinician or participant
1-3[b]	Between 12:00am and 11:59pm on the respective day	CRS clinician or participant

[a] Day of study product administration

[b] New or unresolved Solicited AEs present on day 3 are followed until resolution

9.8.1 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, non-exertional dyspnea, non-exertional tachycardia (assessed by CRS staff, not the participant), generalized pruritus, facial flushing, and unexplained diaphoresis. Local symptoms include pain and/or tenderness at the infusion site. Additionally, in participants receiving SC infusions, local pruritus will be assessed. The daily maximum severity reached for each symptom during the assessment period is reported (see HVTN 136/HPTN 092 SSP).

Body temperature is measured by oral or infrared thermometry. All temperatures must be measured by non-axillary 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. If temperature is measured in Fahrenheit, the conversion to Celsius should be documented in the participant's chart note. A measurement is taken once daily during the assessment period and should be repeated if participant is feeling feverish.

9.8.2 Assessment of infusion sites

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. Areas with diameters greater than 5 cm are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

9.9 Visit windows and missed visits

Visit windows are shown in Appendix S, Appendix T, Appendix U, and Appendix V. For a visit window not performed within the window period, a Missed Visit form is completed.

If a participant misses a scheduled visit, the CRS staff should attempt to bring the participant in as soon as possible to complete the required safety assessments and other procedures. The procedures for documenting missed visits and out of window visits are described in the HVTN 136/HPTN 092 SSP.

If a missed visit required study product administration or if study product administration must be permanently discontinued, please refer to Sections 7.3.1 and 7.3.3 for resolution.

9.10 Early termination visit

In the event of early participant termination, site 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), pregnancy testing, social impact assessment, and HIV test (note, for persons who are confirmed pregnant, pregnancy testing is not required, unless clinically indicated). For participants who have a confirmed diagnosis of HIV infection, see Section 9.12.

9.11 Pregnancy

If a participant becomes pregnant during the course of the study, infusions of study product will not 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 site 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.

9.12 HIV infection during the study

If a participant becomes HIV-infected 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 16 weeks following their last study

product administration or their last scheduled protocol clinic visit, whichever comes first. Follow-up duration for participants diagnosed with HIV infection may be adjusted in consultation with the CRS investigator and the HVTN 136/HPTN 092 PSRT (eg, to avoid interference with participant initiation of HIV treatment). At postinfection follow-up visits, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests will be collected (note: 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 N, Appendix O, Appendix P, and Appendix Q). 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 Site Lab Instructions and HVTN 136/HPTN 092 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 J, Appendix K, Appendix L, and Appendix M. For tests performed locally, the local lab may assign appropriate tube types.

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 J, Appendix K, Appendix L, and Appendix M. 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 PGT121.414.LS and VRC07-523LS concentrations

PGT121.414.LS and VRC07-523LS concentrations will be measured in 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 PGT121.414.LS and VRC07-523LS 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 assay

HIV-1–specific nAb assays will be performed on serum samples from study participants taken at post administration timepoint(s) and at baseline. The TZM-bl assay will test neutralization of a panel of mAb-specific viruses (one virus per mAb). The assay will also test the neutralization of a panel of viruses that exhibit a range of known sensitivities to mAbs VRC07-523LS and PGT121.414.LS. These viruses will be selected from a global panel and/or clade-specific panels (80, 86) and may be modified by site-directed mutagenesis to be capable of measuring the activity of each mAb individually.

10.4.1 ADA detection assay

A tiered testing approach will be used to identify and characterize ADAs that may arise. Anti-PGT121.414.LS and VRC07-523LS antibody detection assays 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).

10.4.2 ADA functional assay

A functional ADA assay will be used to characterize any positive activity that is observed in the ADA detection assay. Functional activity will measure a reduction in VRC07-523LS and PGT121.414.LS neutralizing activity against a qualified virus in the TZM-bl assay.

10.5 Monoclonal Ab reaction assays

To investigate mAb 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 136/HPTN 092 SSP for more information.

10.6 Exploratory studies

Samples may be used for other testing and research related to furthering the understanding of HIV immunology, antibody mediated prevention, or vaccines. In addition, cryopreserved samples may be used to perform additional assays to support standardization and validation of existing or newly developed methods.

10.7 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 required by IRB/EC, or RE.

Other use of specimens is defined as studies not covered by the protocol or the informed consent form for the main study (see Appendix D).

This research may relate to HIV, vaccines, monoclonal antibodies, 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 informed consent form, 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 the CRS's IRBs/ECs/REs 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.

10.8 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 136/HPTN 092 PSRT

The HVTN 136/HPTN 092 PSRT is composed of the following members:

- DAIDS medical officer representatives
- Protocol chairs
- Protocol Team leaders
- Core medical monitor
- Clinical safety specialist

The clinician members of the HVTN 136/HPTN 092 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinator, clinical data manager, study product developer representative, clinical trial manager, clinical research manager, and others may also be included in HVTN 136/HPTN 092 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 adverse events requiring expedited reporting to DAIDS. The SMB conducts additional special reviews at the request of the HVTN 136/HPTN 092 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;

- Providing reports of clinical data to appropriate groups such as the HVTN 136/HPTN 092 PSRT and HVTN SMB (see Section 11.1.2);

The roles and responsibilities of the HVTN Clinical Safety Specialist (CSS) or HVTN Core designee in relation to safety monitoring include:

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 136/HPTN 092 PSRT AE review criteria (see Section 11.4);
- Notifying CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Section 11.4);
- Querying CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 136/HPTN 092 PSRT.

11.2 Safety reporting

11.2.1 Submission of safety forms to SDMC

Site 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 site holiday closure, site staff must submit the data by the end of the 5th day (local time) after receiving the information even if this day is a holiday.

For example: If the site becomes aware of an AE on Thursday (Day 0), the site must submit the data by the end of the next business day, on Friday. If there is a longer site holiday closure, then this AE must be reported no later than the end of the fifth day, Monday (Day 4). If Monday is a holiday as well, all safety forms still need to be submitted by the end of Monday (Day 4).

11.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation participant administered a study product/procedure(s) and which 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). See the HVTN 136/HPTN 092 SSP for further details regarding Solicited and Unsolicited AEs.

The study Unsolicited AE reporting period comprises the entire study period for each individual participant (from enrollment through the last scheduled clinic visit or participant early termination from the study).

All AEs are graded according to the Division of AIDS (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, except:

- 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 136/HPTN 092 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);

- mAb 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 US DHHS (Version 5.0. Published November 27, 2017, available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. **S**ee also HVTN 136/HPTN 092 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); (2) if the AE meets the criteria for a safety pause/prompt AE review (see Section 11.4).

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/hvtn136hptn092). 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, site investigators are required to submit AE information in accordance with IRB/EC and any applicable RE requirements.

11.2.3 Expedited reporting of adverse events 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 EAE Manual), which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids. The SAE Reporting Category will be used for this study.

The internet-based DAIDS Adverse Experience Reporting System (DAERS) must be used for expedited AE (EAE) reporting to DAIDS. In the event of system outages or technical difficulties, expedited AE reports may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at 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:

- PGT121.414.LS
- VRC-HIVMAB075-00-AB (VRC07-523LS)

While the participant is in the study, 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 will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). In addition, 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

Enrollment in Group 1 and Group 2 will be stepwise by 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 3 participants have been enrolled. In addition to monitoring participant safety throughout the study period, the HVTN 136/HPTN 092 PSRT will review all cumulative safety data available up to and including 2 weeks post product administration. Upon PSRT determination that it is safe to proceed, enrollment in Group 2 will begin (see Table 11-1).

Enrollment in Group 2 will be restricted to a maximum of 1 participant per day across all participating CRSs until a total of 3 participants have been enrolled. In addition to monitoring participant safety throughout the study period, the HVTN 136/HPTN 092 PSRT will review all cumulative safety data available up to and including 2 weeks post product administration. Upon PSRT determination that it is safe to proceed, enrollment in Groups 3 and 4 will begin (see Table 11-1).

If any Grade 3 or higher AEs deemed related to study product are reported in Groups 1 or 2, the HVTN SMB will perform an additional review of these safety data to make the final determination based on safety before proceeding to Groups 3 and 4.

Groups 3 and 4 will be enrolled simultaneously. Enrollment will be restricted to a maximum of 1 participant per day from either of the 2 groups across all participant CRSs until a total of 3 participants in each group have been enrolled.

11.3.2 Safety evaluation for opening enrollment in Part B

In addition to monitoring participant safety throughout the study period, the HVTN 136/HPTN 092 PSRT will review all cumulative safety data available from Groups 1 through 4 up to and including the 2-week visit after study product administration. Based on the assessment of these safety data, the HVTN 136/HPTN 092 PSRT will make a decision regarding the appropriateness of opening enrollment in Part B. The HVTN SMB may perform an additional review of these safety data to make the final determination based on safety for proceeding to Part B (see Table 11-1).

If any Grade 3 or higher AEs deemed related to study product are reported in Groups 1, 2, 3 or 4, the HVTN SMB will perform an additional review of these safety data to make the final determination based on safety for proceeding to Part B.

11.3.3 Safety considerations for Part B

Groups 5 and 6 will enroll simultaneously. Enrollment will be restricted to a maximum of 1 participant per day from either of the 2 groups across all

participant CRSs until a total of 3 participants in each group have been enrolled. In addition to monitoring participant safety throughout the study period, the HVTN 136/HPTN 092 PSRT will review cumulative safety data available on the first 6 participants in Part B (3 participants from Group 5 and 3 participants from Group 6) up to and including the 2-week visit after the first study product administration to determine whether the remaining participants in Groups 5 and 6 can be enrolled (see Table 11-1).

If any Grade 3 or higher AEs deemed related to study product are reported in the first 3 participants in Group 5 or Group 6, the HVTN SMB will perform an additional review of these safety data to make the final determination based on safety for proceeding with enrollment of the remaining 7 participants in Group 5 and Group 6. The HVTN 136/HPTN 092 PSRT may consult with the HVTN SMB on an ad hoc basis for any of the previously described evaluations.

Table 11-1 Summary of planned safety holds

Planned Safety Hold	Timepoint/Data Reviewed	Actions
Planned Safety Hold #1 Part A	Begins 2 weeks after the 3rd participant receives study product in Group 1. Review of all cumulative safety data available for the 3 participants in Group 1 up to and including the 2-week visit after the study product administration.	The PSRT will make a decision based on these safety data regarding the appropriateness of beginning enrollment in Group 2 from a safety perspective.
Planned Safety Hold #2 Part A	Begins 2 weeks after the 3rd participant receives study product in Group 2. Review of all cumulative safety data available for the 3 participants in Group 2 up to and including the 2-week visit after the study product administration.	The PSRT will make a decision based on these safety data regarding the appropriateness of beginning enrollment in Groups 3 and 4 from a safety perspective.
Planned Safety Hold #3 Part A	Begins 2 weeks after all participants receive study product in Group 3 and Group 4 (total of 6 participants). Review of all cumulative safety data available for: • The 6 participants in Groups 3 and 4 up to and including the 2-week visit after the first product administration. • All participants in Part A.	The PSRT will make a decision based on all the safety data from all participants included in Part A regarding the appropriateness of beginning enrollment in Part B from a safety perspective.
Planned Safety Hold #4 Part B	Begins 2 weeks after a total of 6 participants receive study product in Part B (3 participants in Group 5 and 3 participants in Group 6). Review of all cumulative safety data available for the 6 participants in Groups 5 and Group 6 up to and including the 2-week visit after the first study product administration.	The PSRT will make a decision based on these safety data regarding the appropriateness of continuing enrollment and subsequent product administrations in Groups 5 and 6 from a safety perspective.

11.4 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 136/HPTN 092 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 136/HPTN 092 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 Core 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/hvtn136hptn092).

[b] HVTN CSS or HVTN Core designee

[c] Does not include subjective Solicited AEs (infusion site pain and/or tenderness, fatigue/malaise, myalgia, arthralgia, nausea, chills, headache, non-exertional dyspnea, generalized pruritus, local pruritus [SC infusion only], facial flushing, and unexplained diaphoresis).

For all safety pauses, HVTN Core notifies the HVTN 136/HPTN 092 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 Core notifies the SMB.

Once a trial is paused, the HVTN 136/HPTN 092 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of study product administration is appropriate, consulting the SMB if necessary. HVTN Core 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 136/HPTN 092 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 136/HPTN 092 PSRT notification or prompt HVTN 136/HPTN 092 PSRT AE review is triggered, HVTN Core notifies the HVTN 136/HPTN 092 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 136/HPTN 092 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 136/HPTN 092 PSRT (see Section 11.5.2).

11.5 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.

11.5.1 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 136/HPTN 092 PSRT AE review criteria.

11.5.2 Weekly review

During the study product administration phase of the trial, the HVTN 136/HPTN 092 PSRT reviews clinical safety reports on a weekly basis and conducts calls to review the data as appropriate. Following the visit 4 weeks after the final study product administration, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 136/HPTN 092 PSRT. HVTN Core reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the CRS clinic coordinator for verification.

11.6 Study termination

This study may be terminated early by the determination of the HVTN 136/HPTN 092 PSRT, FDA, NIH, 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 (ICHe6), and according to DAIDS, HVTN and HPTN policies and procedures as specified in the network-specific Manuals of Operations, 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;
- Unblinding of staff and participants;
- Quality control;
- Protocol monitoring 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 sub-studies, and
- Destruction of specimens.

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 136/HPTN 092 SSP.

12.1 Social impacts

It is possible that participants' involvement in the study could result in social impacts. For example, a participant's involvement in the study could become known to others, and a social harm may result (ie, because participants could be perceived as being HIV infected or at "high risk" for HIV infection). 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 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. Social impacts will be collected and reported on CRFs during scheduled visits (see Appendix N, Appendix O, Appendix P, and Appendix Q). 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 wellbeing of the participant. 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 site 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 136/HPTN 092 are described below.

Protocol history and modifications

Date: October 8, 2019

Protocol version: 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 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 136/HPTN 092 Special Instructions. Accessible through the HVTN protocol-specific website.

- HVTN 136/HPTN 092 Study Specific Procedures. Accessible through the HVTN protocol-specific website.

- HVTN 136/HPTN 092 Site Lab Instructions. Accessible through the HVTN protocol-specific website.

- HVTN 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/daids-sourcedocpolicy.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 http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

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

15 Acronyms and abbreviations

Ab	antibody
ADA	anti-drug antibodies
ADCC	antibody dependent cell mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
AMP	Antibody Mediated Prevention
ANOVA	analysis of variance
ART	antiretroviral therapy
AUC	area-under-the-curve
AUC-MB	area-under-the-magnitude-breadth curve
β-HCG	beta human chorionic gonadotropin
bnAb	broadly neutralizing HIV-1 antibody
CAB	Community Advisory Board
CATNAP	Compile, Analyze and Tally NAb Panels
CAVD	Collaboration for AIDS Vaccine Discovery
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	confidence interval
Cmax	maximum concentration
CRF	case report form
CRPMC	NIAID Clinical Research Products Management Center
CRS	clinical research site
CSS	Clinical Safety Specialist
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
DLT	dose limiting toxicity
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
ELISA	enzyme-linked immunosorbent assay
Fc	Fragment crystallizable
FcRn	Fc-receptor
FDA	US Food and Drug Administration
Fred Hutch	Fred Hutchinson Cancer Research Center
GCP	Good Clinical Practice

GEE	generalized estimating equation
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
IAVI	International AIDS Vaccine Initiative
IB	Investigator's Brochure
IC	inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	infectious dose
IgG	immunoglobulin G
IL	Interleukin
IM	intramuscular
IND	Investigational New Drug
INF	Interferon
IoR	Investigator of Record
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LOC	Leadership Operations Center
mAb	monoclonal antibody
MAR	missing at random
M-B	Magnitude-Breadth
MCAR	missing completely at random
MITT	modified intent-to-treat
MOP	Manual of Operations
MPER	membrane-proximal external region
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
NOAEL	no-observed-adverse-effect-level
NSAID	non-steroidal anti-inflammatory drugs
OHRP	US Office for Human Research Protections

PAB	DAIDS Pharmaceutical Affairs Branch
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetic
popPK	population PK (pharmacokinetic)
PP	per-protocol
PrEP	pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
RAB	DAIDS Regulatory Affairs Branch
RE	regulatory entity
RSC	DAIDS Regulatory Support Center
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SD	standard deviation
SDMC	statistical and data management center
SHIV	simian-human immunodeficiency virus
SMB	Safety Monitoring Board
SMC	Safety Monitoring Committee
SPT	DAIDS Safety and Pharmacovigilance Team
SSP	Study Specific Procedures
SUSAR	sudden unexpected serious adverse reaction
TB	tuberculosis
TCR	tissue cross reactivity
Tmax	time to Cmax
TNF	Tumor necrosis factor
USP	United States Pharmacopeia
UW-VSL	University of Washington Virology Specialty Laboratory
VCMP	and Vaccine Clinical Materials Program
Vd	volume of distribution
VRC	Vaccine Research Center (NIAID)
VTRB	Vaccine Translational Research Branch

16 Literature cited

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Appendix A Sample informed consent form for Part A (Groups 1-4)

Title: A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusion in healthy, HIV-uninfected adult participants

Protocol number: HVTN 136/HPTN 092

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 the study is to understand how well antibodies against HIV work when given alone and combined with other antibodies. We also want to see if the antibodies are safe to give to people and do not make them too uncomfortable.
- If you choose to join, we will ask you to come to several study visits over about 6-8 months. At one of these visits you will get the study antibody in a vein (by IV infusion) or under the skin (by subcutaneous infusion, called SC). We will take blood from you at each study visit to see how your body responds to the study antibody and how much 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 (many with questions of a personal nature) and you will have physical exams.
- Some general risks of antibodies include fever, chills, shaking, nausea, vomiting, pain, 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 this is the first time the study antibody 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 these general risks.
- We do not expect the study antibody to benefit you in any way.

- Whether to take part in this study is your choice. 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 one of the ways the human body fights infection. Antibodies are natural proteins that the body can make to prevent infectious agents such as bacteria and viruses from making you sick. Researchers can also make antibodies in laboratories and give them to people in a vein (by IV infusion) or under the skin (by subcutaneous infusion, called SC). We will tell you more about these procedures below. Officially approved antibodies have been used successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 32 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. In Part A, we will give different doses of one of the study antibodies by IV or SC. People in Part A will only get the study antibody one time. There will be about 12 people in Part A. When we know that there were no serious health problems in Part A, we will decide whether or not to do Part B. If we decide to do Part B, we will give about 20 more people a combination of both study antibodies by IV or SC. We will give these antibodies three times.

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

1. **We are doing this study to answer several questions.**

   - Is the study antibody safe to give to people?
   - Are people able to take the study antibody without becoming too uncomfortable?
   - How much of the study antibody remains in the body as time passes?
   - How does the body's response change depending on how the study antibody is given?

2. The study antibody cannot give you HIV.

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

3. This study antibody is experimental.

The formal name of the study antibody given in Part A is PGT121.414.LS. From here on, we will call it the study antibody. It is an experimental product. That means we do not know if it will be safe to use in people, or if it will work to prevent HIV infection. The study antibody is used only in research studies. This is the first study testing this antibody in people.

The study antibody was developed by researchers with the Collaboration for AIDS Vaccine Discovery (CAVD).

In laboratory studies, the study antibody attached to HIV. It also prevented infection by many strains of HIV from around the world.

In animal studies, the study antibody protected animals from infection with the animal viruses that are very similar to HIV. The study antibody has also been tested for safety in the laboratory and in animals and it did not cause health problems. Even if something looks like it is safe or works in animals, it may not be true for people.

We do not know if the study antibody will prevent HIV when given to people. It will take many studies to learn if it will be useful for HIV prevention. This study will not answer that question.

Risks of the study antibody:

PGT121.414.LS

Because this is the first time the antibody 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 described below.

PGT121

A similar study antibody called PGT121 was changed to make it last longer in the body, and that new version is what we will use in this study. PGT121 is being tested in a study with HIV-positive and HIV-negative participants. As of March 2019, about 28 HIV-negative people and 20 HIV-positive people have gotten different doses of it.by IV infusions and SC injections, sometimes in combination with other experimental antibodies. Ten other people have gotten a placebo (a liquid with no antibody in it). This study is still going on and we don’t know who

got the study antibody and who got a placebo, or what the safety results are.

General risks of antibodies:

There are different types of antibodies officially approved for use in preventing or treating other diseases. From all of these uses of antibodies, we know that most side effects happen within the first 24 hours. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, fatigue, flushing, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat, or chest pain.

Rarely, some antibodies have caused serious reactions that may be life-threatening. These reactions may include:

- Anaphylaxis – a physical reaction that may include hives or rash, swelling in the mouth and face, low blood pressure, and difficulty breathing, possibly leading to low blood oxygen. This may occur soon after getting an antibody.

- Serum Sickness – a physical reaction that includes developing hives or a rash, fever, big lymph nodes, muscle and joint pains, chest discomfort and shortness of breath. This may occur several days to a few weeks after getting an antibody.

These rare reactions have not been seen in other studies with similar experimental antibodies.

Please tell us if you have ever experienced reactions similar to anaphylaxis or serum sickness, and the cause of the reactions if you remember.

Rarely, antibodies officially approved for treatment of other diseases have been linked to a blood disorder that interferes with blood clotting, to cancer, to damage to the heart muscle, and to the body's immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies with similar experimental antibodies.

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 the study antibodies will stay in the body. We don't know yet how long they will last, but it may be several months.

Joining the study

4. It is completely up to you whether or not you 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 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 one study may not be safe.

Also during the study, you should not donate blood or tissue.

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
- Listening to your heart and lungs
- Feeling your abdomen (stomach and liver)
- Checking your veins to see how easy it might be to start an IV

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. We will also test you for syphilis, hepatitis B, and hepatitis C. We will ask you about medications you are taking. We will ask you personal questions about your HIV risk factors such as sexual behavior, alcohol, and drug use.

If you were assigned female sex at birth, we will test you for pregnancy. If you have had your uterus or ovaries removed (a hysterectomy or oophorectomy), 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 were assigned female sex at birth and could become pregnant, you must agree to use birth control to join this study.**

Site: If you want to include Appendix C, Approved birth control 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 the developing baby. You must agree to use effective birth control from 21 days before your infusion until your participation in the study ends. We will talk to you about effective birth control methods. They are listed on a handout that we will give to you.

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 [#] times over 6-8 months.**

Site: Insert number of visits and range of visit lengths. (There is site-specific variation in screening protocols and in the number of possible follow-up visits between protocol-mandated 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 on the next day, 2 days later, 3 days later, 6 days later, and 2 weeks later to draw your blood. We will do this so that we can look at how your body responds to the study antibody. We will also look at how much of the antibody is in your blood. Visits can last from [#] to [#] hours. Follow-up visits can last 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 main 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, birth control costs for participants assigned female sex at birth who could become pregnant).

US sites: Include the following paragraph:

Payments you receive for being in the study may be taxable. We may need to ask you for your Social Security number for tax reasons.

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

10. We will give you the study antibody by IV infusion or SC infusion.

There are 4 groups in Part A of this study, called Group 1, 2, 3 and 4. Everyone in Part A will get the study antibody one time in different doses. People in Groups 1, 2 and 3 will get the study antibody by IV infusion. People in Group 4 will get the study antibody by SC infusion.

When getting an IV infusion, a sterile needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small container of fluid that contains the study antibody. An IV pump controls how fast the fluid drips from the container, through the tube, into your arm. The infusion will take about one hour.

When getting a subcutaneous infusion, a sterile needle is put under the skin on your abdomen or thigh. A pump similar to an IV pump is used to control how fast the study antibody is injected through the needle. You will get one infusion of the study antibody. The infusion will take about 30 minutes

People in Group 1 will be enrolled first, and the safety will be reviewed before enrollment starts in Group 2. Safety for Group 2 will be reviewed before enrollment begins in Groups 3 and 4. Enrollment in Groups 3 and 4, and whether you get the study antibody by IV or SC, is completely random, like flipping a coin. We have no say in how people are assigned to Groups 3 and 4. Neither do you.

11. You will get an IV infusion or SC infusion of the study antibody at the first visit during the study.

Site: A picture of IV infusion placement has been provided in Appendix E. You may insert it below or give it as a separate document to volunteers if you believe it will be helpful to them. You are not required to do either.

Group	Number of Participants	Dose	Study antibody	At enrollment
1	3	Low	PGT121.414.LS	IV infusion
2	3	Medium	PGT121.414.LS	IV infusion
3	3	High	PGT121.414.LS	IV infusion
4	3	Low	PGT121.414.LS	SC infusion

You will have to wait in the clinic for at least 2 hours after the infusion to see if there are any problems. While you are waiting, we will collect a blood sample one hour after the infusion. Then 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. We will review the diary with you at each visit after getting the study antibody. You will turn in the diary at the day 6 visit. Contact the clinic staff if you have any issues or concerns. 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 getting HIV
- Do physical exams
- Do pregnancy tests if you were assigned female sex at birth
- Ask questions about your health, including medications you may be taking
- Ask questions about any personal problems or benefits you may have 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 130 mL (a little less than 2 tablespoons to a little more than ½ cup). Your body will make new blood to replace the blood we take out. Please tell us if you have blood drawn for other purposes during this study.

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 F and Appendix G, Tables 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. We will counsel you on avoiding HIV.

We will ask you personal questions about your HIV risk factors such as sexual behavior, alcohol, and drug use. We will talk with you about ways to keep your risk of getting HIV low.

14. We will test your samples to see how your immune system responds to the study antibody.

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. 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.

The samples will be tested to:

- Measure how much antibody is in your blood, and
- See how your immune system responds to the study antibody.

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 differences in people's genes can help explain why some people get a disease while others do not. The genetic testing will only involve some of your genes, not all of your genes (your genome). The researchers will study only the genes related to the immune system and HIV and those that affect how people get 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 the study antibody.

The 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 with your permission.

Site: Delete next section if using separate consent for use of samples and information in other studies

15. When samples are no longer needed for this study, the HVTN and HPTN may want to use them in other studies and share them with other researchers.

These samples are 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.

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.

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 the United States.

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.]*

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.

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.

Will the HVTN or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we may not be able to get them back.

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 and HPTN will send your samples to the researcher's location.

What information is shared with HVTN, HPTN or other researchers? The samples and information will be labeled with a code number. The key to the code will stay at this clinic. It will not be shared with the HVTN, HPTN or other researchers. Your name will not be part of the information. However, some

information that we share may be personal, such as your race, ethnicity, sex, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

What kind of studies might be done with my extra samples and information? The studies will be related to HIV, vaccines, monoclonal 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. 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.

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 Institutional Review Board or Ethics Committee
- 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.

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

US sites: Check HIPAA authorization for conflicts with this section.

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 and its study monitors,
- The US Food and Drug Administration,
- Any regulatory agency that reviews clinical trials,
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- Beth Israel Deaconess Medical Center (as part of the Protocol Safety Review Team), and people who work for them,
- The HVTN, HPTN and people who work for them,
- The HVTN Safety Monitoring Board and
- The US Office for Human Research Protections.

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. 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]

US sites: Include the following boxed text. You can remove the box.

We have a Certificate of Confidentiality from the US government, to help protect your privacy. With the certificate, we do not have to release information about

you to someone who is not connected to the study, such as the courts or police. Sometimes we can't use the certificate. Since the US government funds this research, we cannot withhold information from it. Also, you can still release information about yourself and your study participation to others.

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 website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

17. We may stop your infusion or take you out of the study at any time. We may do this even if you want to stay in the study.

This may happen if:

- you do not follow instructions,
- we think that staying in the study might harm you,
- you contract HIV,
- you enroll in a different research study where you get another study product, or
- the study is stopped for any reason.

If we stop your infusion, we may ask you to stay in the study to complete other study procedures.

18. We will not give you an infusion if you become pregnant.

However, if you become pregnant after your infusion, we will encourage you to stay in the study if you choose. We will discuss your study options with you.

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.

19. If you get HIV during the study, we will stop your infusions and take fewer samples, and we will help you get care and support.

We will encourage you to stay in the study for up to 4 months if you choose. We will discuss your study options with you. We will counsel you about having HIV

and about telling your partner(s). We will tell you where you can get support and medical care. *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

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 giving blood and receiving SC infusions:

In this study, we will do some routine medical procedures. These include taking blood from you and giving SC infusions to people in Group 4. These procedures can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, blood clots, forming a bump under the skin, and (rarely) muscle damage, or infection where you got the SC infusion. Giving blood can cause swelling of the vein where the needle is placed, or a low blood cell count (anemia), making you feel tired.

Risks of getting an IV infusion:

Getting an infusion 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/testing HIV antibody positive:

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 are infected with HIV or at high risk 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 infections. We have used several common HIV antibody tests to test samples of blood containing different amounts of another study antibody, VRC07-523LS, that will be used in Part B of this study. These tests show that very high levels of this antibody in the blood can cause positive or uncertain results on a few brands of HIV tests. Such high levels might exist for a short time after a person gets the study antibody. This means that for a few days after getting the antibody, certain HIV tests might say a person is infected with HIV when they really aren't. We don't know if the different brands of tests will have similar results for the study antibody being used in Part A.

Although it has not been seen so far, getting the study antibody may cause common HIV antibody tests to show that someone is HIV-negative, even if they are actually infected.

Because of these risks, you should get HIV tests only at this clinic during the study. Our tests can always detect your true HIV status. 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 because the antibodies do not last in the body for that long.

Embarrassment/anxiety:

You may feel embarrassed when we ask about your HIV risks, 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 are infected with 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 it.

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.

In the very unlikely event that your genetic information becomes linked to your name, a US federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

Unknown risks:

We do not know if the study antibody will increase, decrease, or not change your risk of becoming infected with HIV if exposed. If you get infected with HIV, we do not know how the study antibodies might affect your HIV infection or how long it takes to develop AIDS.

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 that getting the study antibody will 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.

This study may help in the search for a vaccine or other methods to prevent HIV. However, if the study antibody or a related product later gets 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 Participant's Bill of Rights and Responsibilities. We will give you a copy of it.

Leaving the study

23. 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.

We will 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 will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protect your health, but it is up to you whether to complete them.

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

24. 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 antibody and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries if certain conditions are met.

Some of the study product providers may pay medical costs for study-related injuries that are determined to be caused by their own study antibodies. If provider funds are not available or are not enough, or if the injury is determined to be caused by study procedures, the HVTN has limited funds to pay medical costs that it determines are reasonable. *(Sites: insert locale-appropriate medical insurance language in the following sentence)* 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, independent experts will be asked to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

25. 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.

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

Your permissions and signature

Site: Delete this section if using a separate consent for use of samples and information in other studies

26. In Section 15 of this form, we told you about possible other uses of your extra samples and information, outside this study. 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 decision 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, HIV prevention, 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.

27. 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 (Groups 5 and 6)

Title: A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

Protocol number: HVTN 136/HPTN 092

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 the study is to understand how well antibodies against HIV work when given alone and combined with other antibodies. We also want to see if the antibodies are safe to give to people and do not make them too uncomfortable.
- If you choose to join, we will ask you to come to several study visits over about 14-16 months. At 3 of these visits you will get combinations of the study antibodies in a vein (by IV infusion) or under the skin (by subcutaneous infusion, called SC). We will take blood from you at each study visit to see how your body responds to the study antibodies and how much antibodies are 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 (many with questions of a personal nature) and you will have physical exams.
- Some general risks of antibodies include fever, chills, shaking, nausea, vomiting, pain, 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. We think that the risks will be similar to these general risks.
- We do not expect the study antibody to benefit you in any way.

- Whether to take part in this study is your choice. 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 one of the ways the human body fights infection. Antibodies are natural proteins that the body can make to prevent infectious agents such as bacteria and viruses from making you sick. Researchers can also make antibodies in laboratories and give them to people in a vein (by IV infusion) or under the skin (by subcutaneous infusion, called SC). We will tell you more about these procedures below. Officially approved antibodies have been used successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 32 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. In Part A, we gave different doses of one of the study antibodies by IV and SC. People in Part A got the study antibody one time. There were about 12 people in Part A and the results showed that it is safe to move ahead with Part B of the study. In Part B, we will give about 20 more people a combination of both study antibodies by IV and SC. We will give the antibodies three times.

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

1. We are doing this study to answer several questions.

- Are the study antibodies safe to give to people together?
- Are people able to take the study antibodies without becoming too uncomfortable?
- How much of the study antibodies remain in the body as time passes?
- How does the body's response change depending on how the study antibodies are given?

2. The study antibodies cannot give you HIV.

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

3. These study antibodies are experimental.

The formal names of the study antibodies are PGT121.414.LS and VRC07-523LS. From here on, we will call them the study antibodies. They are experimental products. That means we do not know if they will be safe to use in people, or if they will work to prevent HIV infection. These study antibodies are used only in research studies. This is the first study testing PGT121.414.LS in people. VRC07-523LS has been tested in a small number of people in previous studies. This is the first study in people using this combination of antibodies.

The 2 study antibodies were developed by researchers with the Collaboration for AIDS Vaccine Discovery (CAVD) (PGT121.414.LS) and at the Dale and Betty Bumpers Vaccine Research Center in Bethesda, Maryland (VRC07-523LS).

In laboratory studies, these study antibodies attached to HIV. They also prevented infection by many strains of HIV from around the world. Each of the study antibodies was strongest against different strains of HIV. When combined in lab tests, they were able to protect human cells from almost all global strains of HIV.

In animal studies, the study antibodies protected animals from infection with animal viruses that are very similar to HIV. The study antibodies have also been tested for safety in the laboratory and in animal studies, and they did not cause health problems. Even if something looks like it is safe or works in animals, it may not be true for people.

We do not know if the study antibodies will prevent HIV infection when given to people. It will take many studies to learn if they will be useful for HIV prevention. This study will not answer that question.

Risks of the study antibodies:

This section lists the side effects we know about when the antibodies are given individually. There may be side effects that we don't yet know about, or side effects from this combination, even serious ones. We will tell you about any new information that might change your willingness to stay in this study.

<u>PGT121.414.LS</u>

Because this is the first time the antibody 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 described below.

PGT121

A similar study antibody called PGT121 was changed to make it last longer in the body, and that new version is what we will use in this study. PGT121 is being tested in a study with HIV-positive and HIV-negative participants. As of March 2019, about 28 HIV-negative people and 20 HIV-positive people have gotten different doses of it by IV infusions and injections, sometimes in combination with other experimental antibodies. Ten other people have gotten a placebo (a liquid with no antibody in it). This study is still going on and we don't know who got the study antibody and who got a placebo, or what the safety results are.

VRC07-523LS

The VRC07-523LS study antibody was given to 25 people by SC injection or IV infusion in a study at the NIH Clinical Center in Bethesda, Maryland. Two people who got the study antibody by IV had chills, fever, nausea, body aches, rapid heartbeat, and headache. They were given Tylenol and Ibuprofen, and the symptoms went away within 12 hours.

As of October 2018, about 120 more people have gotten this study antibody by IV or SC injection in a clinical trial called HVTN 127/HPTN 087. This study is taking place at clinics in the US and in Switzerland. In this study, the antibody has not made people too uncomfortable or caused serious health problems so far.

A similar study antibody called VRC01 has been given in 20,000 infusions to more than 5000 adults in several studies. Many of these studies are still going on and we don't know who got the study antibody and who got a placebo. After receiving VRC01, many people said they had mild pain, itching, or redness where the IV infusion or SC injection was given to them. Some of these people said they felt like they had the flu afterward, but this feeling lasted a few hours at the most.

General risks of antibodies:

There are different types of antibodies officially approved for use in preventing or treating other diseases. From all of these uses of antibodies, we know that most side effects happen within the first 24 hours. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, fatigue, flushing, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat, or chest pain.

Rarely, some antibodies have caused serious reactions that may be life-threatening. These reactions may include:

- Anaphylaxis – a physical reaction that may include hives or rash, swelling in the mouth and face, low blood pressure, and difficulty breathing, possibly leading to low blood oxygen. This may occur soon after getting an antibody.

- Serum Sickness – a physical reaction that includes developing hives or a rash, fever, big lymph nodes, muscle and joint pains, chest discomfort and shortness of breath. This may occur several days to a few weeks after getting an antibody.

These rare reactions have not been seen in other studies with the antibodies in this study or with similar experimental antibodies.

Please tell us if you have ever experienced reactions similar to anaphylaxis or serum sickness, and the cause of the reactions if you remember.

Rarely, antibodies officially approved for treatment of other diseases have been linked to a blood disorder that interferes with blood clotting, to cancer, to damage to the heart muscle, and to the body's immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies with the antibodies in this study or with similar experimental antibodies.

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 the study antibodies will stay in the body. We don't know yet how long they will last, but it may be several months.

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 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 one study may not be safe.

   Also during the study, you should not donate blood or tissue.

   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
- Listening to your heart and lungs
- Feeling your abdomen (stomach and liver)
- Checking your veins to see how easy it might be to start an IV

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. We will also test you for syphilis, hepatitis B, and hepatitis C. We will ask you about medications you are taking. We will ask you personal questions about your HIV risk factors such as sexual behavior, alcohol, and drug use.

If you were assigned female sex at birth, we will test you for pregnancy. If you have had your uterus or ovaries removed (a hysterectomy or oophorectomy), 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 were assigned female sex at birth and could become pregnant, you must agree to use birth control to join this study.**

Site: If you want to include Appendix C, Approved birth control 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 birth control from 21 days before your first infusion until your participation in the study ends. We will talk to you about effective birth control methods. They are listed on a handout that we will give to you.

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 [#] times over 14-16 months.**

Site: Insert number of visits and range of visit lengths. (There is site-specific variation in screening protocols and in the number of possible follow-up visits between protocol-mandated visits.)

Most of the visits will be 1-2 months apart. After you get the study antibodies, we will ask you to come to the clinic for follow-up visits 1 day later (Group 5 enrollment visit only), 3 days later, 6 days later, and 2 weeks later (Groups 5 and 6) to draw your blood. We will do this so that we can look at how your body responds to the study antibodies. We will also look at how much of the antibodies are in your blood. Visits where you get the study antibodies can last from [#] to [#] hours. Follow-up visits can last 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 main 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, birth control costs for participants assigned female sex at birth who could become pregnant).

US sites: Include the following paragraph:

Payments you receive for being in the study may be taxable. We may need to ask you for your Social Security number for tax reasons.

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

10. **We will give you a combination of two study antibodies by IV infusion or SC infusion.**

There are 2 groups in Part B of this study called Group 5 and 6. Everyone in Part B will get both study antibodies 3 times during the study. People in Group 5 will get the antibodies by IV infusion. People in Group 6 will get the antibodies by SC infusion.

When getting an IV infusion, a sterile needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small container of fluid that contains the study antibody. An IV pump controls how fast the fluid drips from the container, through the tube, into your arm. Each antibody is in a separate container. At the first visit, the infusion will take about one hour for each study

antibody (total of about 2 hours). Other IV infusions will take about 30 minutes for each study antibody (total of about 1 hour).

When getting a subcutaneous infusion, a sterile needle is put under the skin on your abdomen or thigh. A pump similar to an IV pump is used to control how fast the study antibody is injected through the needle. We will administer each antibody as a separate infusion, so you will get 2 infusions of the study antibodies. Each infusion will take about 30 minutes in all visits.

Which group you are in and whether you get the study antibody by IV or SC is completely random, like flipping a coin. We have no say in which group you are assigned to. Neither do you.

11. We will give you the study antibodies on a schedule.

You will get an IV infusion or SC infusion of the study antibodies at three visits during the study.

Site: A picture of IV infusion placement has been provided in Appendix E. You may insert it below or give it as a separate document to volunteers if you believe it will be helpful to them. You are not required to do either.

			Infusion schedule		
Group	**Number of Participants**	**Study antibodies**	**At enrollment**	**At 4 Months**	**At 8 Months**
5	10	PGT121.414.LS + VRC07-523LS	IV infusion	IV infusion	IV infusion
6	10	PGT121.414.LS + VRC07-523LS	SC infusion	SC infusion	SC infusion

You will have to wait in the clinic for at least 2 hours after each infusion to see if there are any problems. While you are waiting, we will collect a blood sample one hour after the infusions. Then 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. We will review the diary with you at each visit after getting the study antibody. You will turn in the diary at the day 6 visit. Contact the clinic staff if you have any issues or concerns. 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 getting HIV
- Do physical exams
- Do pregnancy tests if you were assigned female sex at birth

- Ask questions about your health, including medications you may be taking
- Ask questions about any personal problems or benefits you may have 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 120 mL (a little less than 2 tablespoons to about ½ cup). Your body will make new blood to replace the blood we take out. Please tell us if you have blood drawn for other purposes during this study.

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 H and Appendix I, Tables 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. We will counsel you on avoiding HIV.

We will ask you personal questions about your HIV risk factors such as sexual behavior, alcohol, and drug use. We will talk with you about ways to keep your risk of getting HIV low.

14. We will test your samples to see how your immune system responds to the study antibodies.

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. 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.

The samples will be tested to:

- Measure how much antibody is in your blood, and
- See how your immune system responds to the study antibodies.

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 differences in people's genes can help explain why some people get a disease while others do not. The genetic testing will only involve some of your genes, not all of your genes (your genome). The researchers will study only the genes related to the immune system and HIV and those that affect how people get 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 the study antibodies.

The 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 with your permission.

Site: Delete next section if using separate consent for use of samples and information in other studies

15. When samples are no longer needed for this study, the HVTN and HPTN may want to use them in other studies and share them with other researchers.

These samples are 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.

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.

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 the United States.

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.]*

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.

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.

Will the HVTN or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we may not be able to get them back.

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 and HPTN will send your samples to the researcher's location.

What information is shared with HVTN, HPTN or other researchers? The samples and information will be labeled with a code number. The key to the code will stay at this clinic. It will not be shared with the HVTN, HPTN, or other researchers. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, sex, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

What kind of studies might be done with my extra samples and information? The studies will be related to HIV, vaccines, monoclonal 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. 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.

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 Institutional Review Board or Ethics Committee
- 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.

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

US sites: Check HIPAA authorization for conflicts with this section.

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 and its study monitors,
- The US Food and Drug Administration,
- Any regulatory agency that reviews clinical trials,
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- The Dale and Betty Bumpers Vaccine Research Center, Beth Israel Deaconess Medical Center (as part of the Protocol Safety Review Team), and people who work for them,
- The HVTN, HPTN, and people who work for them,
- The HVTN Safety Monitoring Board and
- The US Office for Human Research Protections.

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. 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]

US sites: Include the following boxed text. You can remove the box.

We have a Certificate of Confidentiality from the US government, to help protect your privacy. With the certificate, we do not have to release information about you to someone who is not connected to the study, such as the courts or police. Sometimes we can't use the certificate. Since the US government funds this research, we cannot withhold information from it. Also, you can still release information about yourself and your study participation to others.

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 website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

17. We may stop your infusion or take you out of the study at any time. We may do this even if you want to stay in the study.

This may happen if:

- you do not follow instructions,
- we think that staying in the study might harm you,
- you contract HIV,

- you enroll in a different research study where you get another study product, or

- the study is stopped for any reason.

If we stop your infusion, we may ask you to stay in the study to complete other study procedures.

18. We will not give you an infusion if you become pregnant.

However, if you become pregnant after your infusion, we will encourage you to stay in the study if you choose. We will discuss your study options with you.

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.

19. If you get HIV during the study, we will stop your infusions and take fewer samples, and we will help you get care and support.

We will encourage you to stay in the study for up to 4 months if you choose. We will discuss your study options with you. We will counsel you about having HIV and about telling your partner(s). We will tell you where you can get support and medical care. *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

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 giving blood (Group 5 and 6) and receiving SC infusions (Group 6):

In this study, we will do some routine medical procedures. These include taking blood from you and giving you SC infusions. These procedures can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, blood clots, forming a bump under the skin, and (rarely) muscle damage, or infection where you got the SC infusion. Giving blood can cause swelling of the vein where the needle is placed, or a low blood cell count (anemia), making you feel tired.

Risks of getting an IV infusion (Group 5):

Getting an infusion 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/testing HIV antibody positive:

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 are infected with HIV or at high risk 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 infections. We have used several common HIV antibody tests to test samples of blood containing different amounts of one of the study antibodies, VRC07-523LS. These tests show that very high levels of this antibody in the blood can cause positive or uncertain results on a few brands of HIV tests. Such high levels might exist for a short time after a person gets the study antibody. This means that for a few days after getting the antibody, certain HIV tests might say a person is infected with HIV when they really aren't. We don't know if the different brands of tests will have similar results for the other study antibody.

Although it has not been seen so far, getting the study antibodies may cause common HIV antibody tests to show that someone is HIV-negative, even if they are actually infected.

Because of these risks, you should get HIV tests only at this clinic during the study. Our tests can always detect your true HIV status. 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 because the antibodies do not last in the body for that long.

Embarrassment/anxiety:

You may feel embarrassed when we ask about your HIV risks, 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 are infected with 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 it.

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.

In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

Unknown risks:

We do not know if the study antibodies will increase, decrease, or not change your risk of becoming infected with HIV if exposed. If you get infected with HIV, we do not know how the study antibodies might affect your HIV infection or how long it takes to develop AIDS.

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 that getting the study antibodies will 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.

This study may help in the search for a vaccine or other methods to prevent HIV. However, if the study antibody or a related product later gets 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 Participant's Bill of Rights and Responsibilities. We will give you a copy of it.

Leaving the study

23. 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.

We will 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 will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protect your health, but it is up to you whether to complete them.

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

24. 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 antibodies and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries if certain conditions are met.

Some of the study product providers may pay medical costs for study-related injuries that are determined to be caused by their own study antibodies. If provider funds are not available or are not enough, or if the injury is determined to be caused by study procedures, the HVTN has limited funds to pay medical costs that it determines are reasonable. *(Sites: insert locale-appropriate medical insurance language in the following sentence)* 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, independent experts will be asked to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

25. 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.

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

Your permissions and signature

Site: Delete this section if using a separate consent for use of samples and information in other studies

26. In Section 15 of this form, we told you about possible other uses of your extra samples and information, outside this study. 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 decision 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, HIV prevention, 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.

27. 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 birth control methods for persons assigned female sex at birth (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 antibody could affect the developing baby.

You must agree to use effective birth control from 21 days before your first study infusion until your participation in the study ends.

Effective birth control means using any of the following methods every time you have sex:

- Birth control drugs that prevent pregnancy—given by pills, shots, patches, vaginal rings, or inserts under the skin;
- Male or female condoms, with or without a cream or gel that kills sperm;
- Diaphragm or cervical cap 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 birth control 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 one 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;
- You only have oral sex; or,
- You are sexually abstinent (no sex at all).

Remember: If you are having sex, male and female condoms are the only birth control methods that also provide protection against HIV and other sexually transmitted infections.

If you join the study, we will test you for pregnancy at some visits, including before each study infusion.

Appendix D Sample consent form for use of samples and information in other studies

Title: A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

Protocol number: HVTN 136/HPTN 092

Site: [Insert site name]

When samples are no longer needed for this study, the HVTN and HPTN may want to use them in other studies and share them with other researchers. These samples are called "extra samples". The HVTN 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 the United States.

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 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 and HPTN 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. The key to the code will stay at this clinic. It will not be shared with the HVTN, or other researchers. 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 product you received and how your body responded to the study product.

9. What kind of studies might be done with my extra samples and information?

The studies will be related to HIV, vaccines, monoclonal 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.

In the very unlikely event that your genetic information becomes linked to your name, a US federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

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 Institutional Review Board or Ethics Committee
- 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 .

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, HIV prevention, 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

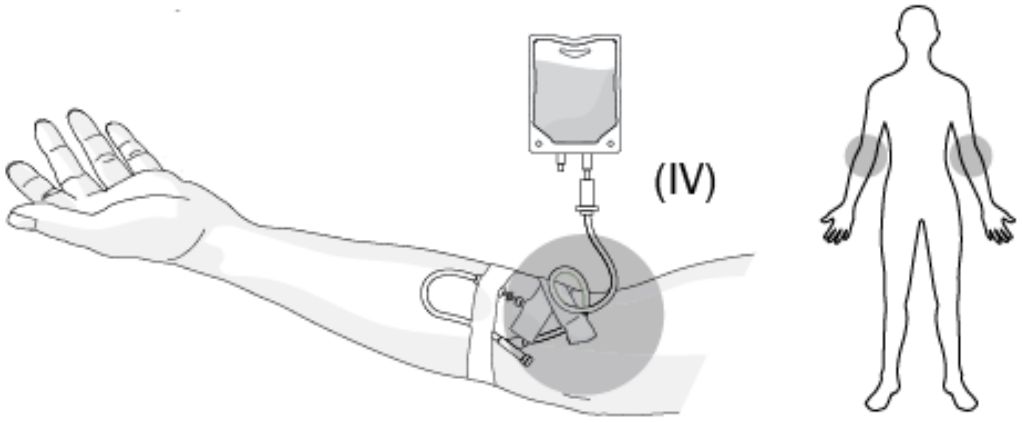
Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

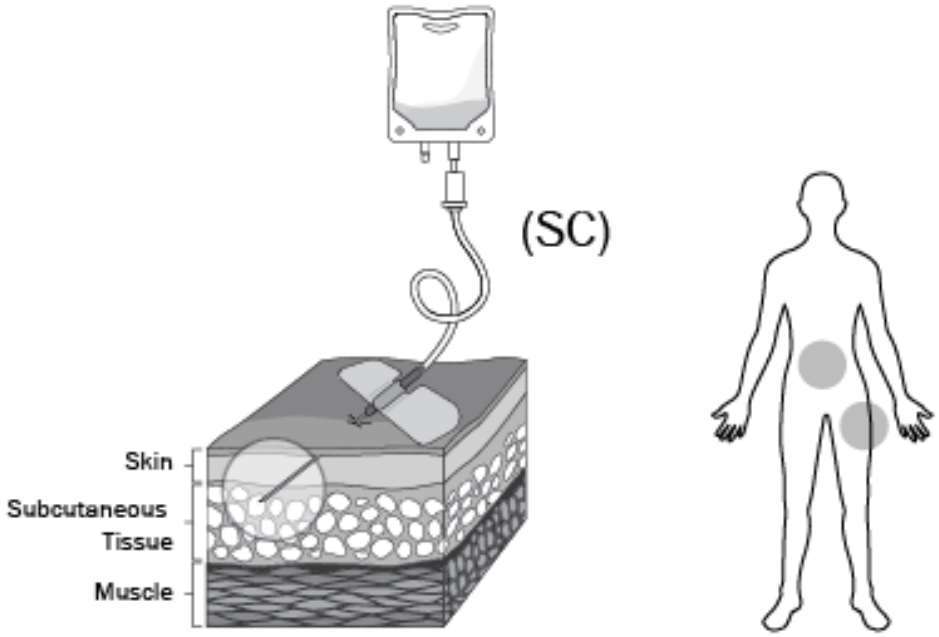
For participants who are unable to read or write, a witness should complete the signature block below:

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 Schematic of IV infusions and SC infusions





Appendix F Table of procedures for Part A Groups 1-3 (for sample informed consent form)

			Time after infusion									
Procedure	Screening visit(s)	Day 0	1 day	2 days	3 days	6 days	2 weeks	1 month	2 months	4 months	6 months	8 months
IV infusion		√										
Medical history	√											
Complete physical	√											√
Brief physical		√	√	√	√	√	√	√	√	√	√	
Urine test	√						√					
Blood drawn	√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test (participants assigned female sex at birth)*	√	√									√	
HIV testing and pretest counseling**	√									√		√
Risk reduction counseling	√	√					√	√	√	√	√	√
Interview/questionnaire(s)	√	√									√	√

* 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.

** We will contact you with results of HIV testing.

Appendix G Table of procedures for Part A Group 4 (for sample informed consent form)

			Time after infusion								
Procedure	Screening visit(s)	Day 0	1 day	2 days	3 days	6 days	2 weeks	1 month	2 months	4 months	6 months
SC infusion		√									
Medical history	√										
Complete physical	√										√
Brief physical		√	√	√	√	√	√	√	√	√	
Urine test	√						√				
Blood drawn	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test (participants assigned female sex at birth)*	√	√								√	
HIV testing and pretest counseling**	√									√	√
Risk reduction counseling	√	√					√	√	√	√	√
Interview/questionnaire(s)	√	√									√

* 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.

** We will contact you with results of HIV testing.

Appendix H Table of procedures for Part B Group 5 (for sample informed consent form)

			Time after first infusion																
Procedure	Screening visit(s)	Day 0	1 day	3 days	6 days	2 weeks	1 month	2 months	3 months	4 months	5 months	6 months	7 months	8 months	9 months	10 months	1 year	1 year & 2 months	1 year & 4 months
IV infusion		√								√				√					
Medical history	√																		
Complete physical	√																		√
Brief physical		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Urine test	√					√					√				√				
Blood drawn	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test (participants assigned female sex at birth)*	√	√								√				√				√	
HIV testing and pretest counseling**	√									√				√			√		√
Risk reduction counseling	√	√				√	√	√	√	√	√	√	√	√	√	√	√	√	√
Interview/questionnaire(s)	√	√								√		√		√			√		√

* 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.

** We will contact you with results of HIV testing.

Appendix I Table of procedures for Part B Group 6 (for sample informed consent form)

			Time after first infusion														
Procedure	Screening visit(s)	Day 0	3 days	6 days	2 weeks	1 month	2 months	3 months	4 months	5 months	6 months	7 months	8 months	9 months	10 months	1 year	1 year & 2 months
SC infusion		√							√				√				
Medical history	√																
Complete physical	√																√
Brief physical		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Urine test	√				√					√				√			
Blood drawn	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test (participants assigned female sex at birth)*	√	√							√				√			√	
HIV testing and pretest counseling**	√								√				√			√	√
Risk reduction counseling	√	√			√	√	√	√	√	√	√	√	√	√	√	√	√
Interview/questionnaire(s)	√	√							√		√		√				√

* 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.

** We will contact you with results of HIV testing.

Appendix J Laboratory procedures for Part A – Groups 1, 2, and 3

Procedure	Ship to[1]	Assay location[2]	Tube Type[4]	Tube size (vol. capacity)[4]	Visit: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
					Day: Screening visit[3]	D0	D1	D2	D3	D6	D14	D28	D56	D84	D112	D140	D168	D196	D224	
					Week:	W0					W2	W4	W8	W12	W16	W20	W24	W28	W32	
						Study Product Administration														
						PGT121.414.LS														
BLOOD COLLECTION																				
Screening/Diagnostic																				
Screening HIV test	Local lab	Local lab	EDTA	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
Syphilis[9]	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HIV diagnostics[7]	UW-VSL	UW-VSL	EDTA	10mL	—	—	—	—	—	—	—	—	—	—	10	—	—	—	20	**30**
Safety labs[10]																				
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	5	5	—	5	—	5	—	5	—	5	—	5	—	5	**45**
Chemistry Panel[5]	Local lab	Local lab	SST	5mL	5	5	5	—	5	—	5	—	5	—	5	—	5	—	5	**45**
Drug concentrations/detection																				
PGT121.414.LS concentration	CSR	HVTN Labs	SST	8.5mL	—	y	y	y	y	y	y	y	y	—	y	—	y	—	y	**0**
Humoral assays																				
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL	—	y	y	y	y	y	y	y	y	—	y	—	—	—	—	**0**
Non-neutralizing antiviral assays	CSR	HVTN Labs	SST	8.5mL	—	y	y	y	y	y	y	y	y	—	y	—	—	—	—	**0**
Anti-Drug Antibody (ADA)																				
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	y	—	—	—	y	**0**
ADA functional assay	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	y	—	—	—	y	**0**
Ab Reaction[11]																				
Tryptase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL	—	See footnote 12	—	—	—	—	See footnote 12			—	See footnote 12	—	See footnote 12	—	See footnote 12	**0**
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL	—	See footnote y	—	—	—	—	—	—	—	—	—	—	—	—	—	**0**
ADA functional assay	CSR	HVTN Labs	SST	8.5mL	—	See footnote y	—	—	—	—	—	—	—	—	—	—	—	—	—	**0**
STORAGE																				
Serum	CSR	—	SST	8.5mL	—	85[14]	42.5	42.5	42.5	42.5	42.5	42.5	42.5	—	42.5	—	42.5	—	42.5	**510**
Visit total					**25**	**95**	**52.5**	**42.5**	**52.5**	**42.5**	**52.5**	**42.5**	**52.5**	**0**	**62.5**	**0**	**52.5**	**0**	**72.5**	**645**
56-Day total[13]					**25**	**120**	**172.5**	**215**	**267.5**	**310**	**362.5**	**405**	**457.5**	**95**	**115**	**62.5**	**115**	**52.5**	**125**	
URINE COLLECTION[10]																				
Urine dipstick[8]	Local lab	Local lab			X	—	—	—	—	—	X	—	—	—	—	—	—	—	—	
Pregnancy test[6]	Local lab	Local lab			X	X	—	—	—	—	—	—	—	—	—	—	X	—	—	

Greyed out visits are not applicable to these groups.

[1] CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA).

[2] HVTN Laboratories include: Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA); Dartmouth College (Hanover, New Hampshire, USA). Non-HVTN laboratories: ARUP Laboratories (Salt Lake City, Utah, USA).

[3] Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[4] Local labs may assign appropriate alternative tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment).

[6] For a participant who was born female (ie, assigned female sex at birth), 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 have undergone total 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 is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 15 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).

[8] And microscopy if needed

[9] .Syphilis testing will be done by serology

[10] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

[11] To investigate 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 HVTN 136/HPTN 092 SSP for more information.

[12] SST blood will be collected at specific timepoints after the onset of any Ab reaction. Refer to the HVTN 136/HPTN 092 SSP for more information.

[13] The 56-day total blood volume does not include up to 34mL 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] Of this volume, 17mL of SST blood will be collected 1 hour after the end of the infusion (see Section 9.3).

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 ADA detection and functional assays (including for any Ab reactions); no separate blood draw is needed.

Appendix K Laboratory procedures for Part A – Group 4

				Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	
				Day:	Screening visit[3]	D0	D1	D2	D3	D6	D14	D28	D56	D84	D112	D140	D168	
				Week:		W0					W2	W4	W8	W12	W16	W20	W24	
						Study Product Administration												
Procedure	**Ship to[1]**	**Assay location[2]**	**Tube Type[4]**	**Tube size (vol. capacity)[4]**		**PGT121.414.LS**												**Total**
BLOOD COLLECTION																		
Screening/Diagnostic																		
Screening HIV test	Local lab	Local lab	EDTA	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HBs Ag/anti-HCV	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	**5**
Syphilis[9]	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HIV diagnostics[7]	UW-VSL	UW-VSL	EDTA	10mL	—	—	—	—	—	—	—	—	—	—	10	—	20	**30**
Safety labs[10]																		
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	5	5	—	5	—	5	—	5	—	5	—	5	**40**
Chemistry Panel[5]	Local lab	Local lab	SST	5mL	5	5	5	—	5	—	5	—	5	—	5	—	5	**40**
Drug concentrations/detection																		
PGT121.414.LS concentration	CSR	HVTN Labs	SST	8.5mL	—	y	y	y	y	y	y	y	y	—	y	—	y	**0**
Humoral assays																		
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL	—	y	y	y	y	y	y	y	y	—	y	—	—	**0**
Non-neutralizing antiviral assays	CSR	HVTN Labs	SST	8.5mL	—	y	y	y	y	y	y	y	y	—	y	—	—	**0**
Anti-Drug Antibody (ADA)																		
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	y	—	—	**0**
ADA functional assay	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	y	—	—	**0**
Ab Reaction[11]																		**0**
Tryptase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL	—	See footnote 12	—	—	—	—	See footnote 12			—	See footnote 12	—	See footnote 12	**0**
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL	—	See footnote y	—	—	—	—	—	—	—	—	—	—	—	**0**
ADA functional assay	CSR	HVTN Labs	SST	8.5mL	—	See footnote y	—	—	—	—	—	—	—	—	—	—	—	**0**
STORAGE																		
Serum	CSR	—	SST	8.5mL	—	85[14]	42.5	42.5	42.5	42.5	42.5	42.5	42.5	—	42.5	—	42.5	**468**
Visit total					**25**	**95**	**52.5**	**42.5**	**52.5**	**42.5**	**52.5**	**42.5**	**52.5**	**0**	**62.5**	**0**	**72.5**	**593**
56-Day total[13]					**25**	**120**	**172.5**	**215**	**267.5**	**310**	**362.5**	**405**	**457.5**	**95**	**115**	**62.5**	**135**	
URINE COLLECTION[10]																		
Urine dipstick[8]	Local lab	Local lab			X	—	—	—	—	—	X	—	—	—	—	—	—	
Pregnancy test[6]	Local lab	Local lab			X	X	—	—	—	—	—	—	—	—	X	—	—	

Greyed out visit are not applicable to these groups.

[1] CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA).

[2] HVTN Laboratories include: Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA); Dartmouth College (Hanover, New Hampshire, USA). Non-HVTN laboratories: ARUP Laboratories (Salt Lake City, Utah, USA).

[3] Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[4] Local labs may assign appropriate alternative tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment).

[6] For a participant who was born female (ie, assigned female sex at birth), 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 have undergone total 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 is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 13 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).

[8] And microscopy if needed.

[9] Syphilis testing will be done by serology.

[10] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

[11] To investigate 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 HVTN 136/HPTN 092 SSP for more information.

[12] SST blood will be collected at specific time points 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 34mL 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] Of this volume, 17mL of SST blood will be collected 1 hour after the end of study product administration (see Section 9.3).

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 ADA detection and functional assays; no separate blood draw is needed.

Appendix L Laboratory procedures for Part B – Group 5

					Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
					Day:	Screening visit[3]	D0	D1	D2	D3	D6	D14	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D336	D392	D448	
					Week:		W0					W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W48	W56	W64	
							Study Product Administration #1									Study Product Administration #2				Study Product Administration #3						
Procedure	**Ship to[1]**	**Assay location[2]**	**Tube Type[4]**	**Tube size (vol. capacity)[4]**			PGT121.414.LS + VRC07-523LS									PGT121.414.LS + VRC07-523LS				PGT121.414.LS + VRC07-523LS						**Total**
BLOOD COLLECTION																										
Screening/Diagnostic																										
Screening HIV test	Local lab	Local lab	EDTA	5mL		5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
Syphilis[9]	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HIV diagnostics[7]	UW-VSL	UW-VSL	EDTA	10mL		—	—	—	—	—	—	—	—	—	—	10	—	—	—	10	—	—	10	—	20	**50**
Safety labs[10]																										
CBC/ Differential	Local lab	Local lab	EDTA	5mL		5	5	—	—	—	—	5	5	5	5	5	5	5	5	5	5	5	5	5	5	**80**
Chemistry Panel[5]	Local lab	Local lab	SST	5mL		5	5	—	—	—	—	5	5	5	5	5	5	5	5	5	5	5	5	5	5	**80**
Drug concentrations/detection																										
PGT121.414.LS, VRC07-523LS concentrations	CSR	HVTN Labs	SST	8.5mL		—	y	y	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	**0**
Humoral assays																										
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL		—	y	y	—	y	y	y	y	y	—	y	y	y	y	y	y	y	y	—	—	**0**
Non-neutralizing antiviral assays	CSR	HVTN Labs	SST	8.5mL		—	y	y	—	y	y	y	y	y	—	y	y	y	y	y	y	y	y	—	—	**0**
Anti-Drug Antibody (ADA)																										
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	—	—	—	—	y	—	—	y	y	—	—	y	y	y	**0**
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	—	—	—	—	y	—	—	y	y	—	—	y	y	y	**0**
Ab Reaction[11]																										
Tryptase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL		—	See footnote 12	—	—	—	—	See footnote 12														**0**
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	—	—	—	—	See footnote y	—	—	—	See footnote y	—	—	—	—	—	**0**
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	—	—	—	—	See footnote y	—	—	—	See footnote y	—	—	—	—	—	**0**
STORAGE																										
Serum	CSR	—	SST	8.5mL		—	85[14]	42.5	—	42.5	42.5	42.5	42.5	42.5	42.5	51[14]	42.5	42.5	42.5	51[14]	42.5	42.5	42.5	42.5	42.5	**824.5**
Visit total						**25**	**95**	**42.5**	**0**	**42.5**	**42.5**	**52.5**	**52.5**	**52.5**	**52.5**	**71**	**52.5**	**52.5**	**53**	**71**	**52.5**	**52.5**	**62.5**	**52.5**	**72.5**	**1049.5**
56-Day total[13]						**25**	**120**	**163**	**163**	**205**	**248**	**300**	**353**	**405**	**157.5**	**176**	**176**	**176**	**105**	**124**	**176**	**176**	**115**	**115**	**125**	
URINE COLLECTION[10]																										
Urine dipstick[8]	Local lab	Local lab				X	—	—	—	—	—	X	—	—	—	—	X	—	—	—	X	—	—	—	—	
Pregnancy test[6]	Local lab	Local lab				X	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	—	X	—	

Greyed out visits are not applicable to this group.

[1]CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA)

[2]HVTN Laboratories include: Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA); Dartmouth College (Hanover, New Hampshire, USA).

Non-HVTN laboratories: ARUP Laboratories (Salt Lake City, Utah, USA)

[3]Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[4]Local labs may assign appropriate alternative tube types for locally performed tests.

[5]Chemistry panels are defined in Section 9.2 (pre-enrollment).

[6]For a participant who was born female (ie, assigned female sex at birth), 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 have undergone total 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 is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 20 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).

[8]And microscopy if needed.

[9]Syphilis testing will be done by serology.

[10]For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

[11]To investigate 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 HVTN 136/HPTN 092 SSP for more information.

[12]SST blood will be collected at specific timepoints after the onset of any Ab reaction. Refer to the HVTN 136/HPTN 092 SSP for more information.

[13]The 56-day total blood volume does not include up to 51mL 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] Of this volume, 17mL of SST blood will be collected 1 hour after the end of the infusion (see Section 9.3).

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 ADA detection and functional assays (including for any Ab reactions); no separate blood draw is needed.

Appendix M Laboratory procedures for Part B – Group 6

					Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
					Day:	Screening visit[3]	D0	D1	D2	D3	D6	D14	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D336	D392	
					Week:		W0					W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W48	W56	
							Study Product Administration #1									**Study Product Administration #2**				**Study Product Administration #3**					
Procedure	**Ship to[1]**	**Assay location[2]**	**Tube Type[4]**	**Tube size (vol. capacity)[4]**			**PGT121.414.LS + VRC07-523LS**									**PGT121.414.LS + VRC07-523LS**				**PGT121.414.LS + VRC07-523LS**					**Total**
BLOOD COLLECTION																									
Screening/Diagnostic																									
Screening HIV test	Local lab	Local lab	EDTA	5mL		5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
Syphilis[9]	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HIV diagnostics[7]	UW-VSL	UW-VSL	EDTA	10mL		—	—	—	—	—	—	—	—	—	—	10	—	—	—	10	—	—	10	20	**50**
Safety labs[10]																									
CBC/ Differential	Local lab	Local lab	EDTA	5mL		5	5	—	—	—	—	5	5	5	5	5	5	5	5	5	5	5	5	5	**75**
Chemistry Panel[5]	Local lab	Local lab	SST	5mL		5	5	—	—	—	—	5	5	5	5	5	5	5	5	5	5	5	5	5	**75**
Drug concentrations/detection																									
PGT121.414.LS, VRC07-523LS concentrations	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	**0**
Humoral assays																									
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	y	y	y	y	y	—	y	y	y	y	y	y	y	y	—	**0**
Non-neutralizing antiviral assays	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	y	y	y	y	y	—	y	y	y	y	y	y	y	y	—	**0**
Anti-Drug Antibody (ADA)																									
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	—	—	—	—	y	—	—	y	y	—	—	y	y	**0**
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	y	—	—	—	—	—	—	—	—	y	—	—	y	y	—	—	y	y	**0**
Ab Reaction[11]																									
Tryptase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL		—	See footnote 12	—	—	—	—	See foootnote 12													**0**
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	—	—	—	—	See footnote y	—	—	—	See footnote y	—	—	—	—	**0**
ADA functional assay	CSR	HVTN Labs	SST	8.5mL		—	See footnote y	—	—	—	—	—	—	—	—	See footnote y	—	—	—	See footnote y	—	—	—	—	**0**
STORAGE																									
Serum	CSR	—	SST	8.5mL		—	85[14]	—	—	42.5	42.5	42.5	42.5	42.5	42.5	51[14]	42.5	42.5	42.5	51[14]	42.5	42.5	42.5	42.5	**739.5**
Visit total						**25**	**95**	**0**	**0**	**42.5**	**42.5**	**52.5**	**52.5**	**52.5**	**52.5**	**71**	**52.5**	**52.5**	**104**	**71**	**52.5**	**52.5**	**62.5**	**72.5**	**1005.5**
56-Day total[13]						**25**	**120**	**120**	**120**	**163**	**205**	**258**	**310**	**363**	**157.5**	**176**	**176**	**176.0**	**156**	**175**	**227**	**176**	**115**	**135**	
URINE COLLECTION[10]																									
Urine dipstick[8]	Local lab	Local lab				X	—	—	—	—	—	X	—	—	—	—	X	—	—	—	X	—	—	—	
Pregnancy test[6]	Local lab	Local lab				X	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	

Greyed out visits are not applicable to this group.

[1]CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA)

[2]HVTN Laboratories include: Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA); Dartmouth College (Hanover, New Hampshire, USA).

[3]Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[4]Local labs may assign appropriate alternative tube types for locally performed tests.

[5]Chemistry panels are defined in Section 9.2 (pre-enrollment).

[6]For a participant who was born female (ie, assigned female sex at birth), 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 have undergone total 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 is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 19 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).

[8]And microscopy if needed.

[9]Syphilis testing will be done by serology.

[10]For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

[11]To investigate 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 HVTN 136/HPTN 092 SSP for more information.

[12]SST blood will be collected at specific time points 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 51mL 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]Of this volume, 17mL of SST blood will be collected 1 hour after the end of study product administration (see Section 9.3).

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 ADA detection and functional assays; no separate blood draw is needed.

Appendix N Procedures at CRS for Part A Groups 1 – 3

Visit	01[1]	02[2]	03	04	05	06	07	08	09	10	11	12	13	14	15	Post
Day:		D0	D1	D2	D3	D6	D14	D28	D56	D84	D112	D140	D168	D196	D224	
Week:		W0	W0	W0	W0	W0	W2	W4	W8	W12	W16	W20	W24	W28	W32	
Procedure	Scr	Inf														
Study procedures																
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Infusion	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Solicited AE assessment[3]	—	X	X	X	X	—	—	—	—	—	—	—	—	—	—	—
Abbreviated physical exam	—	X	X	X	X	X	X	X	X	—	X	—	X	—	—	—
Risk reduction counseling[4]	X	X	—	—	—	—	X	X	X	—	X	—	X	—	X	—
Contraception status assessment[5]	X	X	—	—	—	—	X	X	X	—	X	—	X	—	X	—
Social impact assessment	—	X	—	—	—	—	X	X	X	—	X	—	X	—	X	—
Behavioral risk assessment questionnaire[6]	X	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Social impact assessment questionnaire	—	—	—	—	—	—	—	—	—	—	—	—	X	—	X	—
Acceptability questionnaire	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Concomitant medications	X	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	—	X	—
HIV infection assessment[7]	X	—	—	—	—	—	—	—	—	—	X	—	—	—	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	—	—	—	—	—	X	—	—	X
Sample Collection[8]	X	X	X	X	X	X	X	X	X	—	X	—	X	—	X	—

Greyed out visits are not applicable to these groups.

[1] Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[2] Specimens collected at Day 0 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 24 hours prior to study product administration with negative results received prior to study product administration.

[3] Solicited AE assessments performed daily for at least 3 days following study product administration. CRS staff to contact participant to review and report Solicited AEs following the Solicited AE period (see the HVTN 136/HPTN 092 SSP).

[4] Includes transmission risk reduction counseling for HIV-infected participants.

[5] Contraception status assessment is required only for participants who were assigned female sex at birth and who are capable of becoming pregnant.

[6] Not applicable to HIV-infected participants.

[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 infection.

[8] For specimen collection requirements, see Appendix J.

Appendix O Procedures at CRS for Part A Group 4

Visit	01[1]	02[2]	03	04	05	06	07	08	09	10	11	12	13	Post
Day:		D0	D1	D2	D3	D6	D14	D28	D56	D84	D112	D140	D168	
Week:		W0	W0	W0	W0	W0	W2	W4	W8	W12	W16	W20	W24	
Procedure	Scr	Inf												
Study procedures														
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Infusion	—	X	—	—	—	—	—	—	—	—	—	—	—	—
Solicited AE assessment[3]	—	X	X	X	X	—	—	—	—	—	—	—	—	—
Abbreviated physical exam	—	X	X	X	X	X	X	X	X	—	X	—	—	—
Risk reduction counseling[4]	X	X	—	—	—	—	X	X	X	—	X	—	X	—
Contraception status assessment[5]	X	X	—	—	—	—	X	X	X	—	X	—	X	—
Social impact assessment	—	X	—	—	—	—	X	X	X	—	X	—	X	—
Behavioral risk assessment questionnaire[6]	X	—	—	—	—	—	—	—	—	—	—	—	X	—
Social impact assessment questionnaire	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Acceptability 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 infection assessment[7]	X	—	—	—	—	—	—	—	—	—	X	—	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	—	—	—	—	—	X	X
Sample Collection[8]	X	X	X	X	X	X	X	X	X	—	X	—	X	—

Greyed out visits are not applicable to these groups.

[1] Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[2] Specimens collected at Day 0 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 24 hours prior to study product administration with negative results received prior to study product administration.

[3] Solicited AE assessments performed daily for at least 3 days following study product administration. CRS staff to contact participant to review and report Solicited AEs following the Solicited AE period (see the HVTN 137/HPTN 092 SSP).

[4] Includes transmission risk reduction counseling for HIV-infected participants.

[5] Contraception status assessment is required only for participants who were assigned female sex at birth and who are capable of becoming pregnant.

[6] Not applicable to HIV-infected participants.

[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 infection.

[8] For specimen collection requirements, see Appendix K.

Appendix P Procedures at CRS for Part B Group 5

Visit	01[1]	02[2]	03	04	05	06	07	08	09	10	11[3]	12	13	14	15	16	17	18	19	20	Post
Day:		D0	D1	D2	D3	D6	D14	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D336	D392	D448	
Week:		W0	W0	W0	W0	W0	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W48	W56	W64	
Procedure	Scr	Inf 1									Inf 2				Inf 3						
Study procedures																					
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Infusion[4]	—	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	—	—	—	—
Solicited AE assessment[4]	—	X	X	—	X	—	—	—	—	—	X	—	—	—	X	—	—	—	—	—	—
Abbreviated physical exam	—	X	X	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—	—
Risk reduction counseling[5]	X	X		—	—	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Contraception status assessment[6]	X	X	—	—	—	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Social impact assessment	—	X		—			X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Behavioral risk assessment questionnaire[7]	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Social impact assessment questionnaire	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—	X	—	X	—
Acceptability questionnaire	—	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	—	—	—	—
Concomitant medications	X	X	X	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Intercurrent illness/Unsolicited adverse experience	—	X	X	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
HIV infection assessment[8]	X	—	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X
Sample collection[9]	X	X	X	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—

Greyed out visits are not applicable to this group.

[1] Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[2] Specimens collected at Day 0 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 24 hours prior to study product administration with negative results received prior to study product administration.

[3] Blood draws required at study product administration visit must be performed prior to administration of study product; however, it is not necessary to have results prior to administration, except for results of a serum pregnancy test, if indicated. Lab tests may be drawn with the 3 days prior to study product administration.

[4] Solicited AE assessments performed daily for at least 3 days following study product administration. CRS staff to contact participant to review and report Solicited AEs following the Solicited AE period (see the HVTN 136/HPTN 092 SSP).

[5] Includes transmission risk reduction counseling for HIV-infected participants.

[6] Contraception status assessment is required only for participants who were assigned female sex at birth and who are capable of becoming pregnant.

[7] Not applicable to HIV-infected participants.

[8] 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 infection.
[9] For specimen collection requirements, see Appendix L.

Appendix Q Procedures at CRS for Part B Group 6

Visit	01[1]	02[2]	03	04	05	06	07	08	09	10	11[3]	12	13	14	15	16	17	18	19	Post
Day:		D0	D1	D2	D3	D6	D14	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D336	D392	
Week:		W0	W0	W0	W0	W0	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W48	W56	
Procedure	Scr	Inf 1									Inf 2				Inf3					
Study procedures																				
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Infusion[4]	—	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	—	—	—
Solicited AE assessment[4]	—	X	—	—	X	—	—	—	—	—	X	—	—	—	X	—	—	—	—	—
Abbreviated physical exam	—	X	—	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—	—
Risk reduction counseling[5]	X	X	—	—	—	—	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Contraception status assessment[6]	X	X	—	—	—	—	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Social impact assessment	—	X	—	—			X	X	X	X	X	X	X	X	X	X	X	X	X	—
Behavioral risk assessment questionnaire[7]	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		X	—
Social impact assessment questionnaire	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—		X	—
Acceptability questionnaire	—	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	—	—	—
Concomitant medications	X	X	—	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Intercurrent illness/Unsolicited adverse experience	—	X	—	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
HIV infection assessment[8]	X	—	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	X
Sample collection[9]	X	X	—	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—

Greyed out visits are not applicable to this group.

[1] Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

[2] Specimens collected at Day 0 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 24 hours prior to study product administration with negative results received prior to study product administration.

[3] Blood draws required at study product administration visit must be performed prior to administration of study product; however, it is not necessary to have results prior to administration, except for results of a serum pregnancy test, if indicated. Lab tests may be drawn with the 3 days prior to study product administration.

[4] Solicited AE assessments performed daily for at least 3 days following study product administration. CRS staff to contact participant to review and report Solicited AEs following the Solicited AE period (see the HVTN 136/HPTN 092 SSP).

[5] Includes transmission risk reduction counseling for HIV-infected participants.

[6] Contraception status assessment is required only for participants who were assigned female sex at birth and who are capable of becoming pregnant.

[7] Not applicable to HIV-infected participants.
[8] 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 infection.
[9] For specimen collection requirements, see Appendix M.

Appendix R HVTN low risk guidelines for the US

The following are intended as guidelines for the investigator to help identify potential vaccine trial participants at "low risk" for HIV infection. These guidelines are based on behaviors within the last 6-12 months prior to enrollment; however, it may be appropriate to consider a person's behavior over a longer period of time than specified to assess the person's likelihood of maintaining low risk behavior. Some volunteers may not be appropriate for enrollment even if they meet these guidelines. These guidelines should be supplemented and interpreted with local epidemiologic information about HIV prevalence in your area and community networks. The investigator may review the risk level of any volunteer with the site PI and/or the Protocol Safety Review Team.

A volunteer may be appropriate for inclusion if he/she meets these guidelines:

1. Sexual behaviors

In the **last 12 months** did not:

- Have oral, vaginal or anal intercourse with an HIV-infected partner, or a partner who uses injection drugs
- Give or receive money, drugs, gifts or services in exchange for oral, vaginal or anal sex

AND

In the **last 6 months** has abstained from penile/anal or penile/vaginal intercourse, OR

In the **last 6 months**:

- Had 4 or fewer partners of the opposite birth sex for vaginal and/or anal intercourse, OR

Is an MSM (person born male with partner(s) born male) who, in the **last 12 months**:

- Had 2 or fewer MSM partners for anal intercourse and had no unprotected anal sex with MSM, OR
- Had unprotected anal intercourse with only 1 MSM partner, within a monogamous relationship lasting at least 12 months (during which neither partner had any other partners). If the monogamous relationship ended, the volunteer may then have had protected anal intercourse with 1 other MSM partner (total 2 or fewer partners in the last 12 months).

Is a transgender person, regardless of the point on the transition spectrum, having sex with men (born male) and/or other transgender persons, who in the **last 12 months**:

- Had 2 or fewer partners for anal or vaginal intercourse, and had no unprotected anal or vaginal sex, OR
- Had unprotected anal or vaginal intercourse sex with 1 partner only within a monogamous relationship lasting at least 12 months (during which neither partner had any other partners). If the monogamous relationship ended, may then have had protected anal or vaginal sex with 1 other partner (total 2 or fewer partners in the last 12 months).

AND

Uses or intends to use condoms in situations which may include penile/anal or penile/vaginal intercourse with new partners of unknown HIV status, occasional partners, partners outside a primary relationship, and/or partners known to have other partners.

2. Non-sexual behaviors

In the **last 12 months** did not:

- Inject drugs or other substances without a prescription
- Use cocaine, methamphetamine, or excessive alcohol, which in the investigator's judgment, rendered the participant at greater than low risk for acquiring HIV infection. The investigator's judgment should consider local epidemiologic information about HIV prevalence in the area and community networks.

A volunteer is NOT appropriate for inclusion if he/she:

Acquired an STI (i.e. new infection) in the last 12 months:

- Syphilis
- Gonorrhea
- Non-gonococcal urethritis
- Herpes Simplex Virus type 2 (HSV2)
- Chlamydia
- Pelvic inflammatory disease (PID)
- Trichomonas
- Mucopurulent cervicitis
- Epididymitis
- Proctitis
- Lymphogranuloma venereum
- Chancroid
- Hepatitis B

Appendix S Visit Windows for Part A Groups 1-3

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day	Upper Target Day	Upper Allowable Window
01.0	Screening	-56	-		-	-
02.0	**Enrollment[1] Infusion**	-	-	0	-	-
03.0	1 day post infusion	-	-	1	-	-
04.0	2 days post infusion	-	-	2	-	-
05.0	3 days post infusion	-	-	3	-	-
06.0	6 days post infusion	-2	-	6	-	+2
07.0	2 weeks post infusion	-7	-3	14	+3	+7
08.0	4 weeks post infusion	-7	-3	28	+3	+7
09.0	8 weeks post infusion	-7	-3	56	+3	+7
10.0						
11.0	16 weeks post infusion	-7	-3	112	+3	+7
12.0						
13.0	24 weeks post infusion	-7	-3	168	+3	+7
14.0						
15.0	Final Visit 32 weeks post infusion	-14	-7	224	+7	+14

[1]Screening should be conducted within 56 days of Enrollment (Infusion.)

Appendix T Visit Windows for Part A Group 4

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day	Upper Target Day	Upper Allowable Window
01.0	Screening	-56	-		-	-
02.0	**Enrollment[1] Infusion**	-	-	0	-	-
03.0	1 day post infusion	-	-	1	-	-
04.0	2 days post infusion	-	-	2	-	-
05.0	3 days post infusion	-	-	3	-	-
06.0	6 days post infusion	-2	-	6	-	+2
07.0	2 weeks post infusion	-7	-3	14	+3	+7
08.0	4 weeks post infusion	-7	-3	28	+3	+7
09.0	8 weeks post infusion	-7	-3	56	+3	+7
10.0						
11.0	16 weeks post infusion	-7	-3	112	+3	+7
12.0						
13.0	Final Visit 24 weeks post infusion	-7	-3	168	+3	+7

[1]Screening should be conducted within 56 days of Enrollment (Infusion).

Appendix U Visit Windows for Part B Group 5

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day	Upper Target Day	Upper Allowable Window
01.0	Screening	-56	-		-	-
02.0	**Enrollment[1] Infusion #1**	-	-	0	-	-
03.0	1 day post infusion #1[2]	-	-	1	-	-
04.0		-	-		-	-
05.0	3 days post infusion #1[2]	-	-	3	-	-
06.0	6 days post infusion #1[2]	-2	-	6	-	+2
07.0	2 weeks post infusion #1[2]	-7	-3	14	+3	+7
08.0	4 weeks post infusion #1[2]	-7	-3	28	+3	+7
09.0	8 weeks post infusion #1[2]	-7	-3	56	+3	+7
10.0	12 weeks post infusion #1[2]	-7	-3	84	+3	+7
11.0	**Infusion #2**	-14	-7	112	+7	+14
12.0	4 weeks post infusion #2[2]	-7	-3	140	+3	+7
13.0	8 weeks post infusion #2[2]	-7	-3	168	+3	+7
14.0	12 weeks post infusion #2[2]	-7	-3	196	+3	+7
15.0	**Infusion #3**	-14	-7	224	+7	+14
16.0	4 weeks post infusion #3[2]	-7	-3	252	+3	+7
17.0	8 weeks post infusion #3[2]	-7	-3	280	+3	+7
18.0	16 weeks post infusion #3[2]	-7	-3	336	+3	+7
19.0	24 weeks post infusion #3[2]	-7	-3	392	+3	+7
20.0	Final Visit 32 weeks post infusion #3[2]	-14	-7	448	+7	+14

[1]Screening should be conducted within 56 days of Enrollment (Infusion #1).
[2]Postinfusion visits are scheduled according to date of the prior infusion visit.

Appendix V Visit Windows for Part B Group 6

Visit Number	Visit Type	Lower Allowable Window	Lower Target Day	Target Day	Upper Target Day	Upper Allowable Window
01.0	Screening	-56	-		-	-
02.0	**Enrollment[1] Infusion #1**	-	-	0	-	-
03.0		-	-		-	-
04.0		-	-		-	-
05.0	3 days post infusion #1[2]	-	-	3	-	-
06.0	6 days post infusion #1[2]	-2	-	6	-	+2
07.0	2 weeks post infusion #1[2]	-7	-3	14	+3	+7
08.0	4 weeks post infusion #1[2]	-7	-3	28	+3	+7
09.0	8 weeks post infusion #1[2]	-7	-3	56	+3	+7
10.0	12 weeks post infusion #1[2]	-7	-3	84	+3	+7
11.0	**Infusion #2**	-14	-7	112	+7	+14
12.0	4 weeks post infusion #2[2]	-7	-3	140	+3	+7
13.0	8 weeks post infusion #2[2]	-7	-3	168	+3	+7
14.0	12 weeks post infusion #2[2]	-7	-3	196	+3	+7
15.0	**Infusion #3**	-14	-7	224	+7	+14
16.0	4 weeks post infusion #3[2]	-7	-3	252	+3	+7
17.0	8 weeks post infusion #3[2]	-7	-3	280	+3	+7
18.0	16 weeks post infusion #3[2]	-7	-3	336	+3	+7
19.0	Final Visit 24 weeks post infusion #3[2]	-7	-3	392	+3	+7

[1]Screening should be conducted within 56 days of Enrollment (Infusion #1).
[2]Postinfusion visits are scheduled according to date of the prior infusion visit.

Appendix W Protocol Signature Page

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

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

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Investigator of Record Name (print) Investigator of Record Signature Date

DAIDS Protocol Number: HVTN 136/HPTN 092

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Protocol Date: October 8, 2019