A5377

A Phase I, First-in-Human Study of SAR441236, a Tri-specific Broadly Neutralizing Antibody, in Participants with HIV

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:
National Institute of Allergy and Infectious Diseases

Industry Support Provided by:
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ACTG
AIDS CLINICAL TRIALS GROUP

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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International 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 (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5377@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5377@fstrf.org. A response should generally be received within **1 business day**.

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5377 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the core team.

- Send an e-mail message to actg.corea5377@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to virology or pharmacology laboratory tests, contact the Protocol Virologist or Pharmacologist **listed on the Affiliations tab of the study's web page on the ACTG member website**.

- Send an e-mail message with a cc to: actg.teamA5377@fstrf.org.
- For questions specifically related to processing and transport/shipping of protocol specimens, contact the laboratory technologist (LT) indicated on the current Laboratory Processing Chart (LPC) and cc the study core team: actg.coreA5377@fstrf.org. The phone number for the LT is provided in the LPC and should be used if the processing/shipping question is urgent.

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data managers. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact the data managers **listed on the Affiliations tab of the study's web page on the ACTG member website**.
- For other questions, send an e-mail message to the data managers with a cc to: actg.coreA5377@fstrf.org.
- Include the protocol number, PID, and a detailed question.

Participant Registration/Randomization
For participant registration/randomization questions or problems and study identification number SID lists:

- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

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DMC Portal and Medidata Rave Problems
Contact DMC User Support.
- Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist **listed on the Affiliations tab of the study's web page on the ACTG member website**.
- Send an e-mail message with a cc to: actg.coreA5377@fstrf.org.

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@dlhcorp.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

Product Investigator Brochures
To request copies of the Investigator's Brochure, contact the Division of AIDS (DAIDS) Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation, contact the Clinical Trials Specialist with a cc to the study's core team (actg.corea5377@fstrf.org).

Study Product
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Expedited Adverse Event (EAE) Reporting/Questions
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Protocol-Specific Web Page
More information about protocol management is on the protocol-specific web page (PSWP)

found on the study's web page on the ACTG member website.

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ADA	anti-drug antibody
bNAb	broadly neutralizing antibody
caRNA	HIV-1 cell-associated RNA
CD4bs	CD4 binding site
hsCRP	high sensitivity C-reactive protein
mAb	monoclonal antibody
MPER	HIV-1 gp41 membrane proximal external region
NHP	non-human primate
NOAEL	no observed adverse effect level
PK	pharmacokinetic/s
SC	subcutaneous
SCA	single copy plasma HIV-1 RNA assay

SCHEMA

A5377
A Phase I, First-in-Human Study of SAR441236, a Tri-specific Broadly Neutralizing Antibody, in Participants with HIV

DESIGN	A5377 is a phase I, first-in-human study of SAR441236. It will include three arms with multiple cohorts in each (see Schema Figure 1, Schema Figure 2, and Schema Figure 3, below).
DURATION	**P**articipants will be on study for 24 weeks, with the exception of participants in Cohort 4 who will be on study for **36** weeks **after their final infusion**. **Note that follow-up for all Cohort 4 participants was completed before Version 4.0 of the protocol was opened.**
SAMPLE SIZE	**53-65** evaluable participants: 6 participants each in Cohorts 1-3**, 8, 10, and** 11, **5 participants in Cohort 5, and** 12 participants in Cohort 4**, with the possibility of another 6 participants in Cohort 8. There is also the possibility of enrolling 6 participants in Cohort 7, if criteria are met for this cohort to open (see section 10.4.2)**.
POPULATION	Arm A and Arm C: Adults with HIV-1, 18 to 70 years of age, on suppressive combination antiretroviral therapy (ART) for at least 12 months, with CD4 count of ≥200 cells/mm^3 and plasma HIV-1 RNA levels <50 copies/mL on any FDA-approved assay with a limit of quantification <50 copies/mL. A single plasma HIV-1 RNA ≥50 but <200 copies/mL at least 6 months prior to screening is permitted if followed within 2 months by an HIV-1 RNA <50 copies/mL. Arm B: Adults with HIV-1, 18 to 70 years of age, with HIV-1 who either have not initiated ART or have stopped ART at least 8 **weeks** prior to study entry. All Arm B participants must intend and be able to initiate or re-initiate combination ART by Day **14** on study.
REGIMEN	Double-blind randomization in Arms A and C **was** 2:1 SAR441236:placebo. Arm B participants will all receive open-label SAR441236. Arm A and Arm C cohorts **were** dosed in ascending order. **Enrollment into these two arms was completed before Version 4.0 of the protocol.** **As of Version 4.0 of the protocol, d**osing in Arm B **will be at up to three doses only: 1 mg/kg (Cohort 5) and** 30 mg/kg (Cohort 8)**, with the possibility of 10 mg/kg (Cohort 7)**. See section 3.0 for more information.

Arm A (ART-treated, virologically suppressed**; enrollment and treatment in the cohorts listed below was completed before Version 4.0 of the protocol.**)

Cohort 1: 1 mg/kg of SAR441236 or saline placebo administered as a single intravenous (IV) infusion. Cohort 1 enrollment was completed under Version 2.0.

Cohort 2: 3 mg/kg of SAR441236 or saline placebo administered as a single IV infusion. Cohort 2 enrollment was completed under Version 2.0.

Cohort 3: 10 mg/kg of SAR441236 or saline placebo administered as a single IV infusion. Cohort 3 enrollment was completed under Version 2.0.

Cohort 4: 30 mg/kg of SAR441236 or saline placebo administered as an IV infusion every 12 weeks for a total of four infusions. Cohort 4 enrollment was opened under Version 2.0.

Arm B (HIV viremic)

Cohort 5: 1 mg/kg of SAR441236 administered as a single IV infusion. **Enrollment, treatment, and follow-up in this cohort was completed before Version 4.0 of the protocol.**

Cohort 8: 30 mg/kg of SAR441236 administered as a single IV infusion.

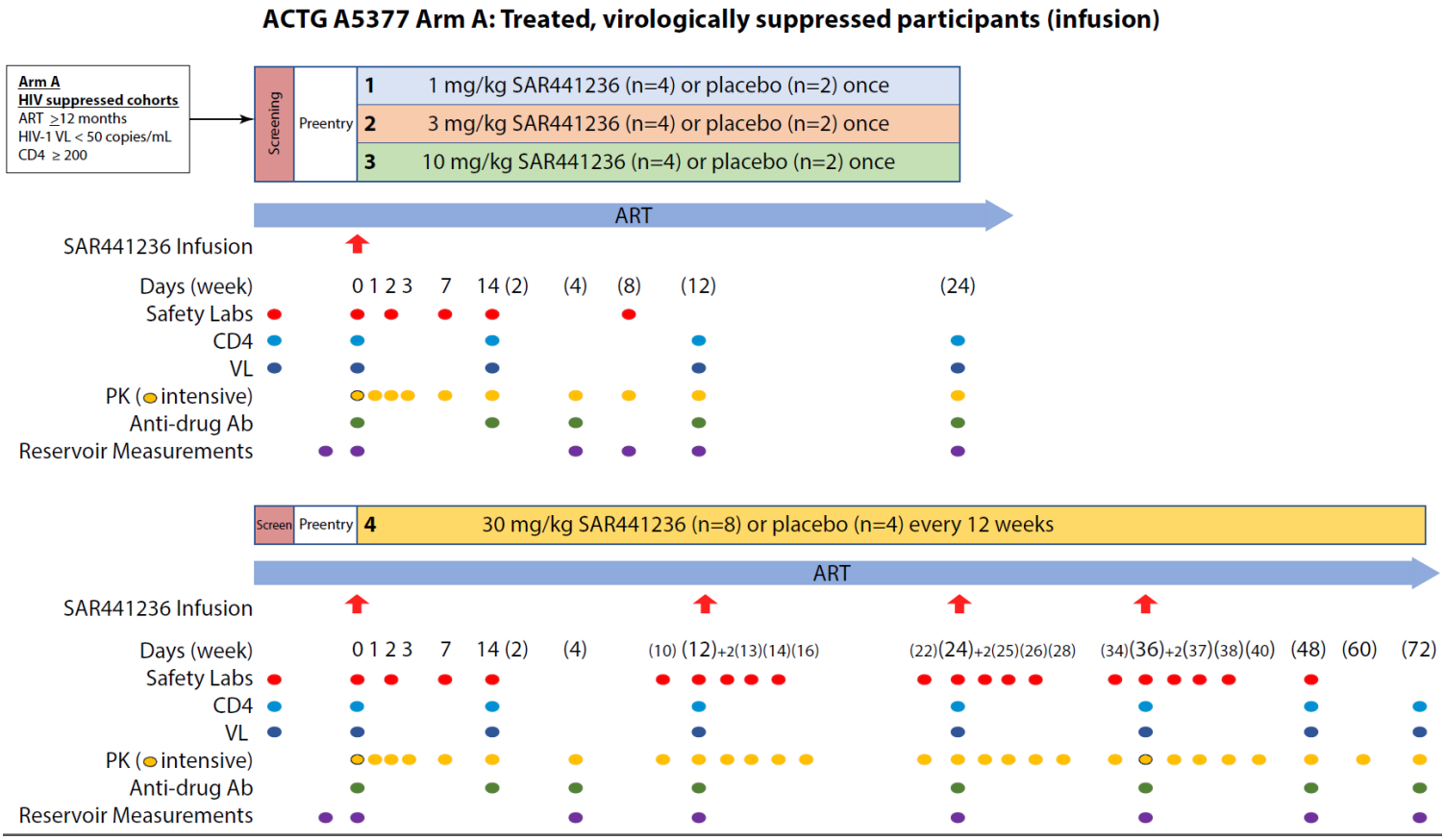
Cohort 7: 10 mg/kg of SAR441236 administered as a single IV infusion.
NOTE: This cohort will only be opened if protocol-specified criteria are met (see section 10.4.2).

Under Version 4.0 of the protocol, participants in Arm B will initiate or re-initiate combination non-study-provided ART on Day **14**.

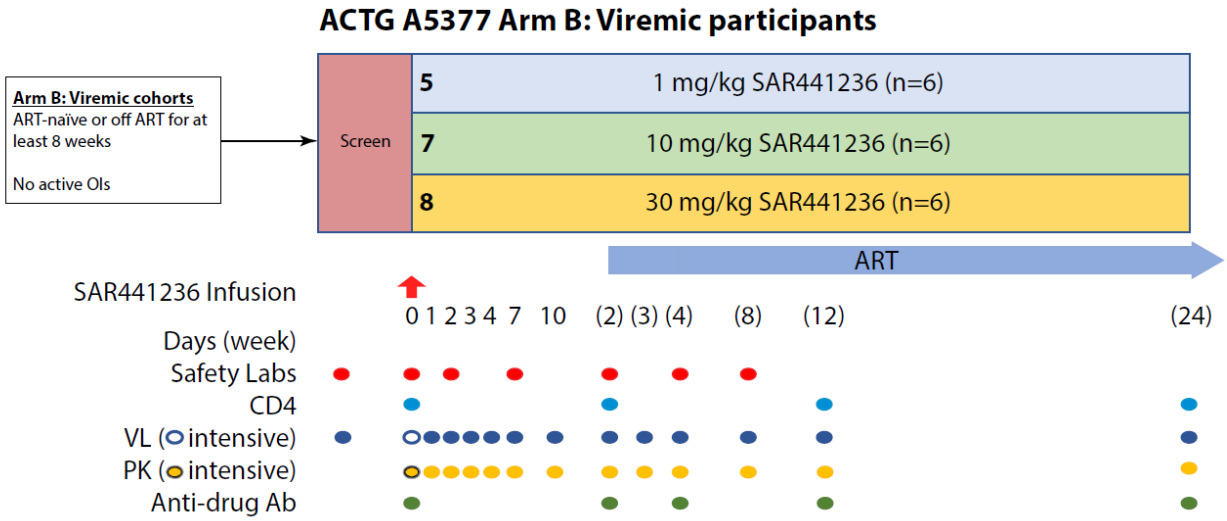
Arm C (ART-treated, virologically suppressed; **enrollment and treatment in the cohorts listed below was completed before Version 4.0 of the protocol.**)

Cohort 10: 0.3 mg/kg of SAR441236 or saline placebo administered once via a single subcutaneous (SC) injection on a single day.

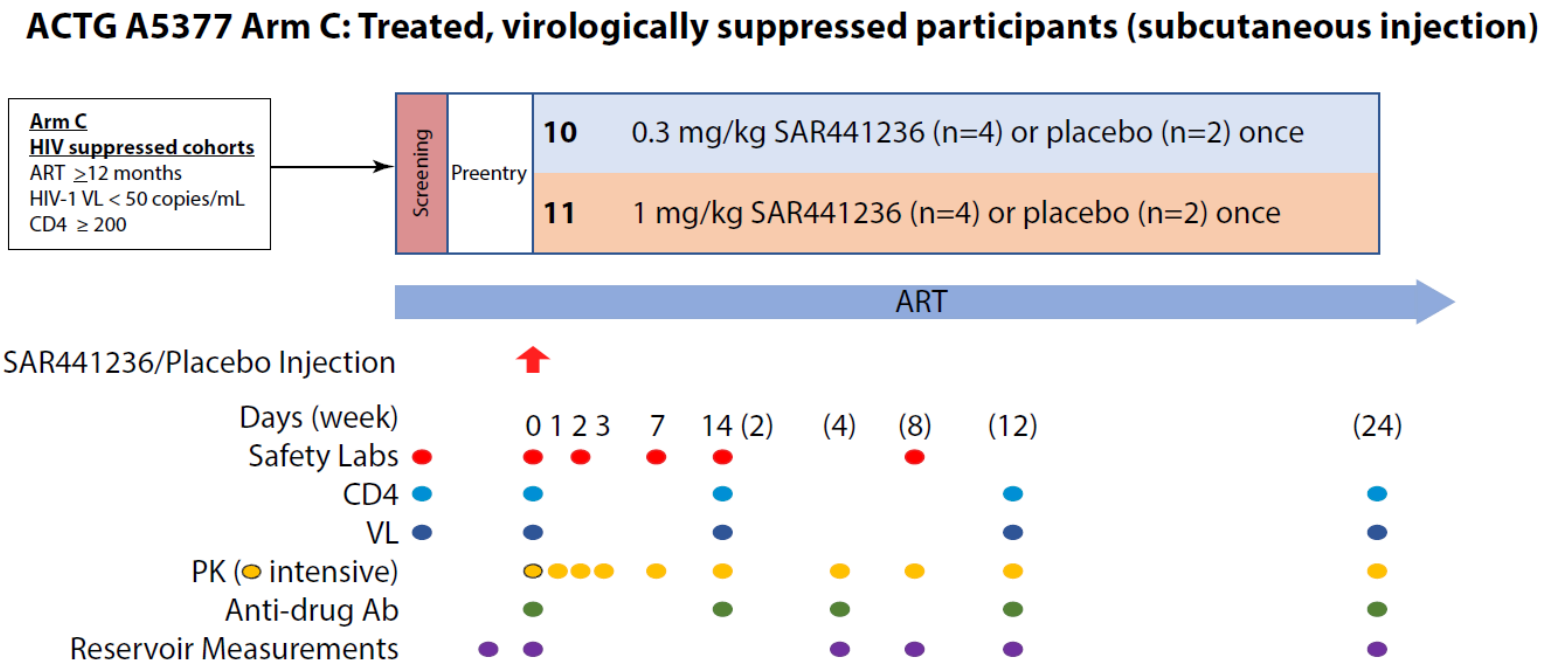
Cohort 11: 1 mg/kg of SAR441236 or saline placebo administered once via single or multiple SC injections on a single day.



Schema Figure 1: Arm A



Schema Figure 2: Arm B



Schema Figure 3: Arm C

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Infusion of SAR441236 is safe and well-tolerated at the proposed doses.

1.1.2 The pharmacokinetics (PK) of SAR441236 after infusion of a single dose is similar in viremic and virologically suppressed participants with HIV.

1.1.3 SAR441236 has dose-dependent anti-HIV-1 activity in viremic participants with HIV.

1.1.4 Subcutaneous injection of SAR441236 is safe and well-tolerated at the proposed doses.

1.2 Primary Objectives

1.2.1 To evaluate the safety and tolerability of single doses of SAR441236 in virologically suppressed participants with HIV receiving ART (Arm A, Cohorts 1-3, and Arm C, Cohorts 10 and 11) and in viremic participants with HIV (Arm B), and of multiple doses in virologically suppressed participants with HIV who are receiving ART (Arm A, Cohort 4).

1.2.2 To evaluate the PK of single doses of SAR441236 in virologically suppressed participants with HIV receiving ART (Arm A, Cohorts 1-3 and Arm C, Cohorts 10 and 11), and in viremic participants with HIV (Arm B), and of multiple doses in virologically suppressed participants with HIV who are receiving ART (Arm A, Cohort 4).

1.2.3 To evaluate the antiviral activity of a single dose of SAR441236 in viremic participants with HIV at Day 7 after the infusion (Arm B).

1.3 Secondary Objectives

1.3.1 To evaluate the dynamics of plasma HIV-1 RNA decay in viremic participants receiving SAR441236 (Arm B).

1.3.2 To evaluate the antiviral activity of a single dose of SAR441236 at Day 14 and Day 28 and the maximum antiviral activity of a single dose of SAR441236 from baseline to Day 28 in viremic participants (Arm B).

1.3.3 To evaluate if anti-SAR441236 antibodies are induced after single or multiple doses.

1.3.4 To evaluate the effects of single and multiple doses of SAR441236 on $CD4^+$ T cell counts.

1.3.5 To establish concentration (or dose)-response relationships between SAR441236 exposure and changes in plasma HIV-1 RNA from entry to week 4 (or viral load nadir) in Arm B.

1.4 Exploratory Objectives

1.4.1 To evaluate the baseline phenotypic HIV-1 susceptibility to SAR441236.

1.4.2 To assess HIV-1 *env* genotypic changes and to evaluate the phenotypic change in HIV-1 susceptibility to SAR441236 from baseline to Day 28 in participants with detectable viremia at Day 28.

1.4.3 To perform deep sequencing of HIV-1 *env* in baseline samples from participants whose virus isolates demonstrate decreased susceptibility to SAR441236 over 28 days.

1.4.4 To assess baseline virus susceptibility to SAR441236 in virologically suppressed participants with HIV who are receiving ART by full-length HIV-1 DNA *env* cloning and sequencing.

1.4.5 To evaluate the ability of SAR441236 to modulate HIV-specific $CD8^+$ cytotoxic T cell responses and humoral immunity.

1.4.6 To evaluate the effects of SAR441236 on the HIV-1 reservoir.

1.4.7 To evaluate whether administration of SAR441236 to virologically suppressed participants with HIV who are taking ART results in a decrease in low-level viremia as measured by the single copy plasma HIV-1 RNA assay (SCA).

1.4.8 To explore the relationship between inflammatory state, including high sensitivity C-reactive protein (hsCRP), and the PK of SAR441236.

2.0 INTRODUCTION

2.1 Background

Broadly neutralizing HIV-1 antibodies (bNAbs) develop in some people with HIV, usually after several years of infection. However, it remains a challenge to elicit bNAbs by vaccination because broad and potent HIV-1 neutralization often requires unusual antibody characteristics, such as long hypervariable loops, interaction with glycans, and substantial somatic mutation. Thus, there is an interest in passive immunization with monoclonal antibodies (mAbs) modeled on these naturally occurring bNAbs to prevent, treat, and potentially cure HIV-1 infection, as well as an interest in studying bNAbs to inform and expedite the development of an HIV-1 vaccine that may elicit such antibodies.

Over the past decade, several bNAbs have been discovered and isolated, and their HIV-1 target sites and mechanisms of their HIV-1 neutralization have been elucidated [Zhou 2010, Gray 2009, Walker & Simek 2010, Stamatatos 2009, Mascola 2013, Kwong 2012, McCoy 2017, Burton 2016]. These efforts have informed the design of recombinant protein immunogens that can elicit bNAbs through a vaccine [Kwong 2012, Walker & Burton 2010, Burton 2012, Burton 2005, Fauci 2016, Haynes 2017] and they have set the stage for an evaluation of these antibodies' potential to contribute to HIV-1 prevention (i.e., passive immunization or antibody-mediated prevention), to treatment, and possibly to cure [Halper-Stromberg 2016, Pegu 2015, Sloan 2015, Caskey 2016, Margolis 2017]. Results from early phase human clinical trials using different classes of bNAbs such as those targeting the CD4 binding site (CD4bs, e.g., VRC01, 3BNC117) and the V3 loop (10-1074 and PGT121) have been encouraging, demonstrating the potential for and challenges of developing anti-HIV-1 bNAbs as preventative and therapeutic agents [Ledgerwood 2015, Bar 2016, Caskey 2015, Caskey 2017].

In people with HIV, single infusions of bNAbs have demonstrated antiviral activity and can reduce plasma virus loads [Caskey 2015, Caskey 2017, Lynch 2015]. However, virus variants that are resistant to the single bNAb emerge quickly and therefore limit the activity and therapeutic potential of bNAb monotherapy [Bar 2016, Caskey 2015, Caskey 2017, Lynch 2015, Scheid 2016]. In the context of treatment interruptions, a modest delay of viral rebound was observed when single bNAbs were infused after antiretroviral drugs were discontinued in previously suppressed individuals with HIV [Bar 2016, Caskey 2015, Caskey 2017, Lynch 2015, Schoofs 2016, Scheid 2016]. Improved neutralizing antibody activity in treated individuals was observed [Schoofs 2016]. IV doses of bNAbs used in clinical studies have varied over a concentration range from 1 to 40 mg/kg, administered either as single or repeated infusions. The testing of bNAb doses over a wide concentration range optimizes the PK modeling of these compounds. In the ongoing antibody-mediated prevention (AMP) studies for HIV prevention, IV VRC01 doses of 10 mg/kg and 30 mg/kg are being evaluated; ongoing phase I studies of PGT121 test IV doses of 3, 10, and 30 mg/kg. A recent dose escalation study of VRC01-LS, a bNAb with an Fc modification that increases antibody half-life (similar to SAR441236), studied IV doses of 5, 20, and 40 mg/kg [Gaudinski 2018].

As new bNAbs are identified with increasing breadth and potency, researchers have started testing combination bNAb approaches. In monkeys, the combination of PGT121 and PGDM1400 provided 100% protection against a virus challenge [Julg 2017] and a phase I human study of this bNAb combination in IV doses of 3-30 mg/kg is underway. In laboratory experiments that examined the neutralizing activities of double, triple, and quadruple mAb combinations targeting different HIV-1 envelope (env) epitopes, antibodies directed to the CD4bs, the variable loop-region glycan, and the gp41 membrane proximal external region (MPER) provided optimal neutralization [Kong 2015].

SAR441236 is an engineered tri-specific bNAb produced by Sanofi that combines the CD4bs specificity of VRC01-LS, the V1/V2 glycan-directed binding of PGDM1400, and the gp41 MPER binding of 10E8v4-variant into one antibody molecule. This tri-specific bNAb neutralizes 204 of 208 (98%) viruses from a standard neutralization panel, and

provided 100% protection to non-human primates against intra-rectal challenge by a mixture of SHIVs, each resistant to one of the bNAb components [Xu 2017]. A5377, the first-in-human study will determine the safety, PK and anti-HIV-1 activity of SAR441236 in participants with HIV on stable, suppressive antiretroviral therapy (ART) and in treatment-naïve participants with HIV. Treatment-naïve participants will initiate ART within 28 days after study entry. Data from the START and TEMPRANO trials suggest that participants who delay the start of ART for 28 days are unlikely to be at increased risk for morbidity or mortality [Lundgren 2015, Danel 2015]. In addition, viremic A5377 participants will have received SAR441236, which has demonstrated potent anti-HIV-1 activity thus far. Participants who do not have a decrease in plasma HIV-1 RNA of at least 0.5 $\log_{10}$ copies/mL by Day 14 will initiate ART before Day 28.

In addition to evaluating the antiviral effect of SAR441236, there is interest in assessing whether it has a vaccinal effect. The passive administration of mAbs for cancer therapy (e.g., rituximab) clears tumor cells through antibody-dependent cell-mediated cytotoxicity (ADCC) but can also induce an anti-tumor T cell memory response, a phenomenon known as the vaccinal effect [DiLillo 2015]. Whether anti-HIV-1 bNAb therapy may induce long-lasting T cell responses in people with HIV is not known. Passive dual bNAb immunotherapy was recently demonstrated to induce T cell immunity in a non-human primate SHIV model [Nishimura 2017]. Moreover, infusion of singe doses of bNAb 3BNC117 resulted in production of antibodies which enhance neutralization activity against autologous virus in viremic individuals with HIV [Schoofs 2016].

Integration of multiple bNAb specificities into a single mAb may improve efficacy
In light of the genetic diversity and viral escape mechanisms of HIV-1 and early human clinical trial results with mAbs for treatment, it is worthwhile to consider using a combination approach. As with antiretroviral therapy, combinations of mAbs may reduce the likelihood of viral escape and increase neutralization breadth, the latter likely critical for treatment and prevention. Combining multiple bNAbs with specificities against different HIV-1 env epitopes into a single molecule has the potential to improve efficacy, simplify prevention and treatment regimens (possibly improving adherence), and streamline the regulatory pathway to a licensed drug.

SAR441236 is a single mAb that features the characteristics of three bNAbs
To test this concept, integration of different classes of anti-HIV bNAbs was carried out using Sanofi's proprietary trispecific antibody platform (Figure 2.1-1).

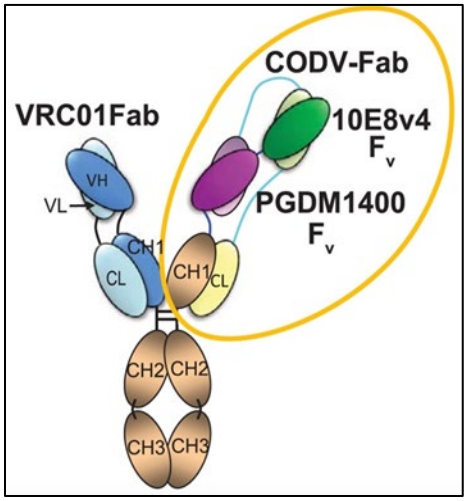


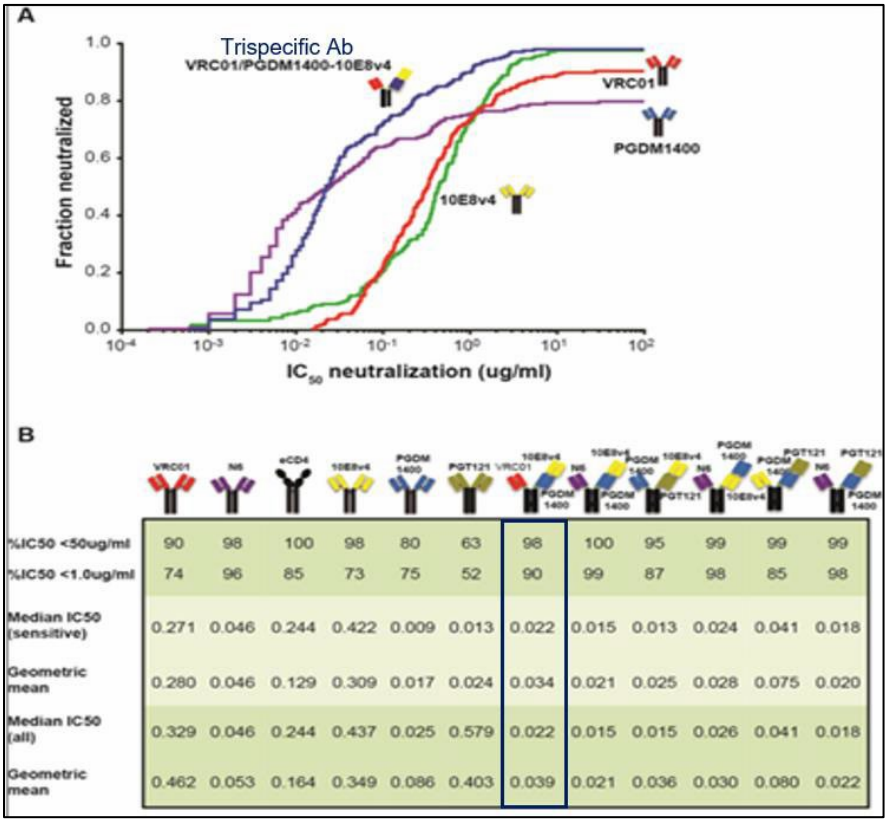
Figure 2.1-1 Configuration of the trispecific antibody. The structure is color-coded by parental antibody. Dark shades refer to heavy chain while pastels indicate light chain peptides. CODV – cross-over dual variable; Fab – fragment antigen binding.

A trispecific platform was chosen to improve the potency and breadth of neutralization. Structural modifications helped ensure that binding affinity and other properties of each component of the trispecific antibody was comparable to that of the parental Fab [Xu 2017].

The classes of mAbs that were evaluated included CD4-binding site (VRC01, VRC07, N6), the membrane proximal external region (MPER) (10E8, 10E8v4), V2-directed (PGT128, PGDM1400), and V3-directed (PGT121). SAR441236, the combination of VRC01/PGDM1400-10E8v4 with the LS Fc modification for half-life extension, was identified as the lead compound based on its neutralizing breadth, potency, persistence (e.g., half-life), solubility, and manufacturability [Xu 2017].

SAR441236 is a potent, broadly neutralizing trispecific mAb

In an assay evaluating the ability of SAR441236 to neutralize 208 HIV-1 viruses covering globally circulating strains, this trispecific bNAb demonstrated a median IC_{50} of 0.022 mcg/mL, with only four resistant viruses, and 90% coverage at IC50 <1.0 mcg/mL (Figure 2.1-2).



	VRC01	N6	eCD4	10E8v4	PGDM 1400	PGT121	VRC01 PGDM 1400	N6 PGDM 1400	10E8v4 PGDM 1400	10E8v4 PGT121	N6 10E8v4	PGDM 1400 PGDM 1400	PGT121 10E8v4	PGT121 N6	PGDM 1400
%IC50 <50ug/ml	90	98	100	98	80	63	98	100	95	99	99	99			
%IC50 <1.0ug/ml	74	96	85	73	75	52	90	99	87	98	85	98			
Median IC50 (sensitive)	0.271	0.046	0.244	0.422	0.009	0.013	0.022	0.015	0.013	0.024	0.041	0.018			
Geometric mean	0.280	0.046	0.129	0.309	0.017	0.024	0.034	0.021	0.025	0.028	0.075	0.020			
Median IC50 (all)	0.329	0.046	0.244	0.437	0.025	0.579	0.022	0.015	0.015	0.026	0.041	0.018			
Geometric mean	0.462	0.053	0.164	0.349	0.086	0.403	0.039	0.021	0.036	0.030	0.080	0.022			

Figure 2.1-2 Breadth and potency of trispecific Abs compared to parental bNAbs and eCD4-Ig against a representative panel of 208 HIV-1 strains. (A) The breadth and potency of trispecific Ab VRC01/PGDM1400-10E8v4 (SAR441236) compared to parental Abs. (B) Summary of neutralization results for the indicated monoclonal and trispecific Abs presented as the percentage of viruses neutralized at IC_{50} of <50 µg/mL and IC_{50} of <1 µg/mL, the median IC_{50} and geometric mean for each Ab against all viruses, and the median IC_{50} and geometric mean for each Ab against viruses sensitive at IC_{50} <50 µg/mL.

An antibody passive transfer/SHIV challenge study was conducted in non-human primates (NHPs) using two mixed SHIV strains (SHIV BaL P4 [resistant to PGDM1400] and SHIV 325C [resistant to VRC01]). NHPs were completely protected up to 100 days after intrarectal challenge at Day 5 post passive transfer of SAR441236 (eight NHPs out of eight), while six out of eight NHPs that received VRC01-LS only and five out of eight NHPs that received PGDM1400-LS only acquired infection when SAR441236 and 2 single bNAbs were administered at 5 mg/kg IV.

SAR441236 immunogenicity

To evaluate the immunogenicity potential of SAR441236 and to measure cytokine release upon stimulation as a marker of CD4+ T cell activation, PBMCs from 22 human donors **without HIV** were co-cultured in with SAR441236 ex vivo. SAR441236 generated positive cytokine responses in 9-23% of donors while VRC01-LS elicited cytokine activation in 18-41% of the donors by the in vitro stimulation. Although these

assays do not fully recapitulate the development of anti-drug antibody (ADA) in vivo, these results, in addition to the clinical immunogenicity profile of other anti-HIV-1 bNAbs, suggest that SAR441236 may pose a low or medium risk of immunogenicity [SAR441236 Investigator's Brochure, June 2018].

SAR441236 pharmacokinetics and dosing

The PK profile of SAR441236 was evaluated in rhesus macaques (n=2). A single dose administration of SAR441236 (10 mg/kg, IV) showed a similar PK profile as that of VRC01-LS (10 mg/kg, IV) up to 21 days [Xu 2017]. The PK were also evaluated in cynomologous monkeys (n=3) following a single administration of SAR441236 (2.5 mg/kg, IV). Based on the allometric scaling, preclinical safety data, and the clinical PK findings of other anti-HIV-1 bNAbs, the proposed dose regimens for this phase 1 study of SAR441236 include 0.3, 1, 3, 10, and 30 mg/kg IV. Establishing the concentration-response relationship (see section 10.4.2) relationship is critical to ensure that the optimum SAR441236 dose is chosen and moved forward into future studies. Preliminary data with neutralizing mAbs directed against other viruses suggest that the PK of antiviral mAbs may be associated more closely with inflammation and increased vascular permeability than with virus load (Sanofi, unpublished data). This observation may explain the PK differences observed for certain anti-HIV-1 bNAbs in HIV-viremic participants versus participants **without HIV** [Caskey 2015]. The clearance of bNAbs is increased in viremic participants but the shape of the PK profiles did not suggest a typical target-mediated drug disposition which would have been associated with the level of HIV-1 virus load. We therefore plan to explore the relationship between inflammatory state (by measuring, for example, hsCRP) and PK data.

In previous versions of the study, we included a dose-escalation design for both virologically suppressed and viremic participants. **Once we had** safety data in virologically suppressed participants on the highest dose (30 µg/kg), we initiate**d** a dose de-escalation design for viremic participants **in Version 3.0** of the study. This approach **was** in keeping with other studies of bNAbs (e.g., ACTG A5340, A5378) [Bar 2016, Chen 2019] and **was considered** the fastest way to ascertain whether the proposed doses of SAR441236 have sufficient antiviral activity. This will not only make the most efficient use of ACTG resources and study product, but will expose the fewest number of participants to low, potentially ineffective doses.

PK modeling and simulation data suggest that the PK profile of SAR441236 is consistent with that of VRC01-LS and VRC07-523LS, bNAbs with the same Fc mutation that prolongs antibody elimination half-life. The simulation data of SAR441236 and the clinical PK profile of VRC01-LS [Gaudinski 2018] and VRC07-523LS [Gaudinski 2019] do not suggest drug accumulation over 3-4 multiple doses administered at 12-week intervals, as is planned in A5377. To define the PK profile of SAR441236 and determine if it is consistent with the simulation and modeling data, we will conduct PK data analyses during the trial.

Toxicity of SAR441236

The toxicity of SAR441236 was evaluated in a single-dose exploratory toxicity study in rats (IV) and a repeat dose GLP toxicity study in rats (IV, SC).

In the single-dose study, 3, 30, or 300 mg/kg IV of SAR441236 was administered in rats followed by a 3-week observation period. The drug was well tolerated with minimal to slight decreased body weight gains at high doses that are considered non-adverse. The dose of 300 mg/kg/adm was considered to be a No Observed Adverse Effect Level (NOAEL).

In the repeat-dose Good Laboratory Practice toxicity study, 30 and 300 mg/kg IV and 30 mg/kg SC of SAR441236 were administered in rats weekly for 3 doses followed by a 2-week recovery period. There were no SAR441236-related adverse clinical signs, including local reaction at the injection sites. Transient clinical signs that were seen at higher doses were most likely associated with the administration of human protein to rodents and were considered non-adverse. Therefore, 300 mg/kg was considered NOAEL after IV administration.

To assess the binding of SAR441236 to any human target, an in vitro immunohistochemistry cross-reactivity study on human tissues was conducted. A total of 38 normal human tissues corresponding to 36 different sections were tested: adrenal gland, blood cells (as part of other tissues), bone marrow, brain (cortex and cerebellum), breast (mammary gland), colon, endothelium (as part of other tissues), esophagus, eye, heart, jejunum, kidney, liver, lung, lymph node, nerve (peripheral), ovary, oviduct (fallopian tube), pancreas, parathyroid gland, pituitary gland, placenta, prostate gland, salivary gland, skeletal muscle, skin, spinal cord, spleen, stomach, testis, thymus, thyroid gland, tonsil, ureter, urinary bladder, and uterus (cervix and endometrium). Under the experimental conditions of the study, no cross-reactivity of biological or toxicological relevance was observed.

SAR441236 contains the antibody specificity of 10E8v4, a bNAb that binds the HIV-1 MPER. In a VRC healthy volunteers study of the investigational antibody 10E8VLS, a bNAb that binds the HIV-1 MPER but with different physiochemical and biologic properties from SAR441236, a 5 mg/kg subcutaneously administered dose resulted in Grade 1 to Grade 3 erythema in seven of eight participants and Grade 1 to Grade 2 induration in four of eight participants. A skin biopsy of the single Grade 3 erythema event was consistent with a non-specific injection site reaction and panniculitis. While 10E8VLS serum concentrations ranged from 10 to 30 mcg/mL, systemic toxicities were not observed. Intravenous dosing of 10E8VLS was not evaluated in this study. Although 10E8VLS and SAR441236 both contain the 10E8v4 paratope, the structure and biochemical properties in 10E8VLS and SAR441236 are different. In A5377, subcutaneous dosing of SAR441236 will begin at doses approximately 16-fold lower than doses studied in the VRC 10E8VLS study. Assessment for injection site reactions is a focus of the post-injection monitoring of Arm C participants.

Subcutaneous injection of SAR441236

A determination of the SC bioavailability is important for the clinical program of SAR441236 as it will support the development of an injection device and may be the preferred route of administration for maintenance. The human bioavailability of subcutaneously delivered mAbs remains hard to predict from nonclinical studies [Viola 2018], justifying the need to evaluate SAR441236 in a clinical context.

The PK of bNAbs have been determined in individuals with and without HIV. A significant increase in clearance was observed in viremic versus non-viremic participants with 10-1074 [Caskey 2017] or 3BNC117 [Caskey 2015]. It was speculated the increased rate of antibody elimination in the presence of HIV-1 could be due to accelerated clearance of antigen–antibody complexes. However, these PK profiles do not display “hockey hook” shapes, which are typical of target-mediated drug disposition [Peletier 2012]. This suggests additional immune mechanisms may be involved that result in increased mAb catabolic clearance, such as inflammation or increased endogenous IgG concentrations competing with FcRn recycling.

Consequently, given the complex interplay between HIV-1 immune activation and mAb absorption, distribution, and elimination, we consider that SAR441236 SC bioavailability should be determined in participants whose immune function has been challenged by HIV-1 antigens. Determination of SAR441236 SC bioavailability in ART-suppressed participants should be more representative of the target population than in participants without HIV.

The doses of 0.3 mg/kg and 1 mg/kg **were** proposed to 1) reduce the number of SC injections given the current formulation concentration and 2) provide sufficient drug exposure to determine the area under the curve (AUC).

The graph below (Figure 2.1-3) shows simulations of SAR441236 plasma concentrations (in µg/mL) following administration of single 0.3 mg/kg and 1 mg/kg doses. The simulation is based on allometric scaling with parameters derived from VRC01-LS PK [Gaudinski 2018].

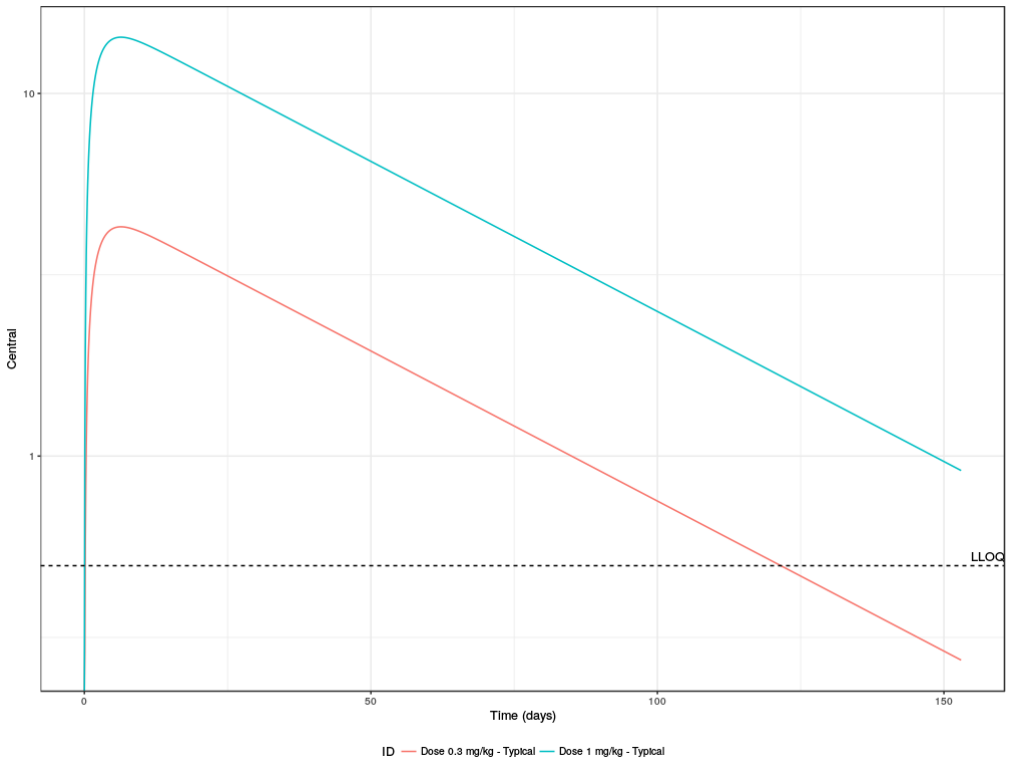


Figure 2.1-3 Simulations of SAR441236 plasma concentrations

Following a single dose administration of SAR441236 at 0.3 mg/kg or 1 mg/kg via the SC route, plasma concentrations should be above the lower limit of quantification (0.5 µg/mL) for approximately 3 months.

Future plans for SAR441236

In the therapeutic setting, SAR441236 is planned for testing in confirmatory trials to determine its ability to maintain long-term viral suppression as a single agent or in combination with other agents and to induce long-term viral remission after combination therapy with other agents being tested in eradication strategies.

Summary

In summary, trispecific mAbs derived from bNAbs with CD4bs, MPER, and V1V2 glycan specificities demonstrated HIV-1 neutralization breadth and potency in vitro and in an animal model. The ability of the investigational SAR441236 trispecific Ab to target three independent epitopes may provide better antiviral activity and increased ability to maintain HIV-1 suppression in humans than an individual mAb, or a combination of single mAbs. Thus, it is scientifically sound to further evaluate SAR441236 in phase 1 human clinical trials to assess its safety (including ADA), PK, and functional activity, and in preparation for further later phase studies testing maintenance strategies, treatment, and functional or sterilizing cure.

2.2 Rationale

This study explores the safety, PK, and anti-HIV-1 activity of the novel trispecific bNAb SAR441236, which may serve as a long-acting alternative to daily oral ART. Susceptibility of plasma HIV-1 to SAR441236 for viremic participants will be tested retrospectively by the Monogram PhenoSense Neutralizing Ab assay. Because this study represents the first-in-human administration of this investigational bNAb, participation is limited to adults from 18 to 70 years of age. The upper age limit of 70 enhances the inclusiveness of the study, reflecting the reality of an aging population of people living with HIV.

In Version 4.0 of the protocol, the inclusion and exclusion criteria have been modified for Arm B participants. Generally, biologic monoclonal antibody therapies have favorable safety profiles. For SAR441236 specifically, no safety signals have been seen with single-dose intravenous administration across a range of 1-10 mg/kg or with four intravenous doses administered every 12 weeks at 30 mg/kg in participants on suppressive ART. The current standard of HIV care recommends HIV treatment begin as soon as possible after an HIV diagnosis**, making enrollment into a first-in-human clinical research protocol challenging**. **Recognizing the existing SAR441236 safety data, the Arm B eligibility criteria have been revised to maximize safety while mitigating barriers to study participation. The team acknowledges the important recent advances in the timing of ART initiation and therefore will encourage screening for A5377 as rapidly as possible following HIV diagnosis and** the administration of **SAR441236** within 1 day after the **screening** visit **[Pilcher 2017, Rosen 2016]**. **Additionally, ART initiation for Arm B participants is now required 14 days rather than 28 days after SAR441236 administration.**

3.0 STUDY DESIGN

A5377 is a phase I, first-in-human, three-arm study of SAR441236.

In Arm A, three successive cohorts of six evaluable (see section 10.4) ART-treated, virologically suppressed participants each **were** randomized 2:1 (four active and two placebo) in a double-blind fashion to receive a single IV dose of SAR441236 or placebo on Day 0. The SAR441236 doses in these cohorts **were**: 1 mg/kg (Cohort 1), 3 mg/kg (Cohort 2), and 10 mg/kg (Cohort 3). After Cohort 1, each subsequent cohort open**ed** for enrollment only after an evaluation of safety outcomes from Day 14 for all participants in the previous cohort and the cumulative data from all the previous cohorts **indicated** that it **was** safe to dose escalate (see section 10.5). **As of November 2021, 24 weeks of follow-up has been completed for a**ll participants in Cohorts 1-3**.**

In Arm A, Cohort 4, a total of 12 **evaluable** participants **were** randomized 2:1 (8 active and 4 placebo) in a double-blind fashion to receive an infusion of 30 mg/kg SAR441236 or placebo once every 12 weeks beginning at entry, for a total of 4 infusions. **As of April 2022, Cohort 4** participants **have completed their** 36 weeks **of follow-up** after the**ir** final infusion.

In Arm B, **up to three** cohorts of six viremic participants each will receive a single IV dose of SAR441236 on Day 0. The SAR441236 doses in these cohorts will be: 1 mg/kg (Cohort 5; enrollment and follow-up in this cohort has been completed), 10 mg/kg (Cohort 7**, possible**)**, and** 30 mg/kg (Cohort 8; this cohort is currently open to enrollment). Participants will be followed for 24 weeks. **As of November 2021, enrollment and follow-up in Cohort 5 has been completed, albeit with 5 rather than 6 participants. Enrollment into Cohort 8 is ongoing. (See section 10.4.2 for further information.)**

In Arm C, two successive cohorts of six evaluable (see section 10.4) ART-treated, virologically suppressed participants each **were** randomized 2:1 (four active and two placebo) in a double-blind fashion to receive a single SC dose of SAR441236 or placebo on Day 0. No more than two Arm C participants **were** dosed in any given week (see section 10.1). The SAR441236 doses in these cohorts **were**: 0.3 mg/kg (Cohort 10) and 1 mg/kg (Cohort 11). Cohort 11 open**ed** for enrollment only after an evaluation of safety outcomes from Day 14 for all participants in Cohort 10 and the cumulative data from all the previous cohorts **indicated** it **was** safe to dose escalate (see section 10.5). **As of December 2021, a**ll Arm C participants **have completed their 24-week** follow-up.

See section 10.1 for information about enrollment of individual cohorts.

For Arm A, across all sites, study treatment at a given dose **was** not administered to a third participant until at least the day after the last of the first two participants **had** received study treatment. No more than two participants receive**d** a given dose on any given day.

For Arm B, across all sites, there will be no restrictions on the number of participants who can be administered a given dose on a single day.

For Arm C, across all sites, study treatment at a given dose **was** not administered to more than two participants within a single week.

Participants in Arm B will initiate or re-initiate non-study-provided combination ART (selected by their primary HIV clinician) on Day **14**.

In all arms and in all cohorts, samples for PK analysis and for measurement of the immunogenicity of SAR441236 will be obtained.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Arm A

NOTE: Arm A closed to enrollment before Version 4.0; no revisions were made to this arm's inclusion or exclusion sections other than re-numbering.

- Inclusion criteria are found in section 4.1
- Exclusion criteria are found in section **4.3**

Arm B

- Inclusion criteria are found in section **4.2**
- Exclusion criteria are found in section **4.4**

Arm C

NOTE: Arm C closed to enrollment before Version 4.0; no revisions were made to this arm's inclusion or exclusion sections other than re-numbering.

- Inclusion criteria are found in section 4.1
- Exclusion criteria are found in sections **4.3** and **4.5**

4.1 Inclusion Criteria, Arms A and C

4.1.1 HIV-1 infection, documented by any licensed rapid HIV1 test or HIV1 enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot, Geenius assay, or a second antibody test by a method other than the initial rapid HIV1and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: The term "licensed" refers to a US FDA-approved kit.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot, Geenius assay, or a plasma HIV-1 RNA viral load.

4.1.2 The following laboratory values obtained within 45 days prior to entry by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent.

- Absolute neutrophil count (ANC) ≥1500 cells/mm^3
- Hemoglobin ≥12.0 g/dL for men and ≥11.0 g/dL for women
- Platelet count ≥120,000/mm^3
- Creatinine clearance (CrCl) >60 mL/min
  - Refer to the calculator located on the FSTRF website (at https://www.frontierscience.org/): Calculated Creatinine Clearance - Cockcroft-Gault Equation (Adult).
- Aspartate aminotransferase (AST) (SGOT) <1.25 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) (SGPT) <1.25 x ULN
- Alkaline phosphatase <2.0 x ULN
- Total bilirubin <1.1 x ULN

4.1.3 Hepatitis C virus (HCV) antibody negative result within 45 days prior to study entry or, for study candidates who are HCV antibody positive (based on testing

performed at any time prior to study entry), a negative HCV RNA result obtained within 45 days prior to study entry.

NOTE: A negative HCV RNA level may result from either spontaneous clearance or from HCV therapy. Participants must have completed any HCV therapy at least 6 months prior to enrollment.

4.1.4 Negative HBsAg result obtained within 45 days prior to study entry, or documented hepatitis B immunity, defined as positive hepatitis B surface antibody testing, at any time.

4.1.5 Female study candidates of reproductive potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL performed at screening and again within 24 hours before study entry by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC)/CLIA-waived test.

NOTE: Reproductive potential is defined as girls who have reached menarche, and women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, and women who have not undergone surgical sterilization, specifically hysterectomy and/or bilateral oophorectomy.

4.1.6 All study candidates must agree not to participate in an assisted conception process (e.g., sperm donation, intrauterine insemination, in vitro fertilization) from screening until 12 weeks after the final study visit.

4.1.7 If participating in sexual activity that could lead to pregnancy, all study candidates must agree to use at least one reliable method of contraception from study entry until 12 weeks after the final study visit. At least one of the following methods must be used appropriately:

- Condoms (male or female) with or without a spermicidal agent. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission.
- Diaphragm or cervical cap with spermicide.
- Intrauterine device.
- Hormone-based contraceptive.

4.1.8 Study candidates who are not of reproductive potential are eligible without requiring the use of a contraceptive method. Acceptable documentation of sterilization, menopause, and reproductive potential is specified below.

- Written documentation or oral communication from a clinician or clinician's staff documented in source documents of one of the following:
  - Physician report/letter
  - Operative report or other source documentation in the patient record

- Discharge summary
- Laboratory report of azoospermia (is required to document successful vasectomy)
- Follicle-stimulating hormone (FSH) measurement elevated into the menopausal range as established by the reporting laboratory.

NOTE A: Female reproductive potential is defined in section 4.1.5.

NOTE B: Male candidates who are not of reproductive potential are defined as having documented azoospermia.

NOTE C: A female study candidate's oral report of her male partner's lack of reproductive potential should be recorded in the source documents if written proof is not available.

4.1.9 Individuals age ≥18 years and ≤70 years at study entry.

4.1.10 Ability and willingness of participant to provide informed consent.

4.1.11 Receiving combination ART for at least 12 months prior to study entry with no changes in ART regimen within the 12 weeks prior to entry.

NOTE A: Use of a two-drug ART regimen within the 12 months prior to entry is exclusionary.

NOTE B: Although ritonavir or cobicistat may be included in a combination ART regimen, neither of these "counts" in a tally of antiretroviral agents.

4.1.12 CD4+ cell count of ≥200 cells/mm^3 obtained within 45 days prior to study entry at any US laboratory that has a CLIA certification or its equivalent.

4.1.13 Within 45 days prior to study entry, plasma HIV-1 RNA <50 copies/mL on any FDA-approved assay with a limit of quantification of <50 copies/mL by a US laboratory that has a CLIA certification or its equivalent.

4.1.14 Within 12 months prior to study entry and before screening, at least one documented plasma HIV-1 RNA <50 copies/mL on any FDA-approved assay with a limit of quantification of <50 copies/mL by a US laboratory that has a CLIA certification or its equivalent.

NOTE: A single plasma HIV-1 RNA ≥50 but <200 copies/mL at least 6 months prior to screening is permitted if followed within 2 months by an HIV-1 RNA <50 copies/mL.

4.2 Arm B Inclusion Criteria

4.2.1 HIV-1 infection, documented by any licensed rapid HIV1 test or HIV1 enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot, Geenius assay, or a second antibody test by a method other than the initial rapid HIV1and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a US FDA-approved kit.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot, Geenius assay, or a plasma HIV-1 RNA viral load.

4.2.2 The following laboratory values obtained within 45 days prior to entry by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent.

- Absolute neutrophil count (ANC) ≥1500 cells/mm^3
- Hemoglobin ≥12.0 g/dL for men and ≥11.0 g/dL for women
- Platelet count ≥120,000/mm^3
- Creatinine clearance (CrCl) >60 mL/min
  - Refer to the calculator located on the FSTRF website (at https://www.frontierscience.org/): Calculated Creatinine Clearance - Cockcroft-Gault Equation (Adult).
- Aspartate aminotransferase (AST) (SGOT) <**2.0** x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) (SGPT) <**2.0** x ULN
- Alkaline phosphatase <2.0 x ULN
- Total bilirubin <**2.0** x ULN

4.2.3 Study candidates **who are able to become pregnant** must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL performed at screening and again within 24 hours before study entry by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC)/CLIA-waived test.

NOTE: **The ability to become pregnant** is defined as **having** reached menarche and not **having** been post-menopausal for at least 24 consecutive months, i.e., **having** had menses within the preceding 24 months, and **not having** undergone surgical sterilization, specifically hysterectomy and/or bilateral oophorectomy.

4.2.4 All study candidates must agree not to participate in an assisted conception process (e.g., sperm donation, intrauterine insemination, in vitro fertilization) from screening until 12 weeks after the final study visit.

4.2.5 If participating in sexual activity that could lead to pregnancy, all study candidates must agree to use at least one reliable method of contraception from study entry until 12 weeks after the final study visit. At least one of the following methods must be used appropriately:

- Condoms with or without a spermicidal agent. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission.
- Diaphragm or cervical cap with spermicide.
- Intrauterine device.
- Hormone-based contraceptive.

4.2.6 Study candidates who are not of reproductive potential are eligible without requiring the use of a contraceptive method. Acceptable documentation of sterilization, menopause, and reproductive potential is specified below.

- Written documentation or oral communication from a clinician or clinician's staff documented in source documents of one of the following:
  - Physician report/letter
  - Operative report or other source documentation in the patient record
  - Discharge summary
  - Laboratory report of azoospermia (is required to document successful vasectomy)
  - Follicle-stimulating hormone (FSH) measurement elevated into the menopausal range as established by the reporting laboratory.

NOTE A: **The ability to become pregnant is defined in** section 4.2.3.

NOTE **B**: A study candidate's oral report of **a** partner's lack of reproductive potential should be recorded in the source documents if written proof is not available.

4.2.7 Individuals age ≥18 years and ≤70 years at study entry.

4.2.8 Ability and willingness of participant to provide informed consent.

4.2.9 Willingness and ability to start or re-start combination ART by or on Day **14** of the study.

4.2.10 For candidates with prior exposure to anti-HIV ART, plasma HIV-1 RNA ≥5000 copies/mL on any FDA-approved assay performed by a US laboratory that has a CLIA certification or its equivalent within 6 months prior to study entry.

4.2.11 For candidates with no prior exposure to ART, documentation of plasma HIV-1 RNA ≥5000 copies/mL on any FDA-approved assay performed by a US laboratory that has a CLIA certification or its equivalent within 6 months prior to study entry, if available.

4.3 Exclusion Criteria, Arms A and C

4.3.1 Breastfeeding or plans to become pregnant.

4.3.2 Receipt of chimeric, humanized or human long-acting mAbs, whether licensed or investigational, within 12 months prior to entry, or receipt of chimeric, humanized or human regular mAbs, whether licensed or investigational, within 6 months prior to entry, unless reviewed and approved by the study's core team.

4.3.3 Known allergy/sensitivity or any hypersensitivity to components of study treatment or its formulation (refer to the product's Investigator's Brochure).

4.3.4 Vaccination within 30 days prior to entry or intent to receive an elective vaccination (e.g., hepatitis A vaccine, travel-related) during the course of the study except as noted in section 5.5.2.

4.3.5 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.3.6 Acute or serious illness requiring systemic treatment and/or hospitalization within 45 days prior to entry.

4.3.7 Diagnosis of AIDS-defining illness using the current list on the US Centers for Disease Control and Prevention (CDC) website within 1 year prior to entry.

4.3.8 Weight >115 kg within 45 days prior to study entry.

4.3.9 Use of maraviroc, ibalizumab, or enfuvirtide at any time.

4.3.10 Within 6 months prior to study entry, any plasma HIV-1 RNA ≥50 copies/mL on any FDA-approved assay with a limit of quantification of <50 copies/mL performed by a US laboratory that has a CLIA certification or its equivalent.

4.4 Arm B Exclusion Criteria

4.4.1 For candidates with prior exposure to ART, use of any ART within the 8 weeks prior to study entry.

4.4.2 For candidates with no prior exposure to ART, use of any HIV pre-exposure prophylaxis within 30 days prior to study entry.

4.4.3 Suspected to be in early or acute stage of HIV infection.

4.4.**4** Breastfeeding or plans to become pregnant.

4.4.**5** Receipt of chimeric, humanized or human long-acting mAbs, whether licensed or investigational, within 12 months prior to entry, or receipt of chimeric, humanized or human regular mAbs, whether licensed or investigational, within 6 months prior to entry, unless reviewed and approved by the study's core team.

4.4.6 Receipt of long-acting cabotegravir within 12 months prior to study entry.

4.4.**7** Known allergy/sensitivity or any hypersensitivity to components of study treatment or its formulation (refer to the product's Investigator's Brochure).

4.4.8 Known chronic hepatitis B.

4.4.**9** Weight >115 kg within 45 days prior to study entry.

4.4.**10** Use of maraviroc, ibalizumab, or enfuvirtide at any time.

4.5 Additional Arm C-specific Exclusion Criterion

4.5.1 Presence of abdominal scarring or tattooing that could interfere with assessment of injection-site reaction.

4.6 Study Enrollment Procedures

4.6.1 Prior to implementation of this protocol, and any subsequent full-version amendments, each site must have the protocol and the protocol consent form approved, as appropriate, by the institutional review board (IRB) responsible for oversight of the study. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites will implement the amendment immediately. Sites will be required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICF(s) will not be reviewed or approved by the DAIDS PRO. Sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the final Amendment

Registration Notification issued by the DAIDS PRO should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The candidate will be asked to read and sign the approved protocol consent form.

For candidates from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the DMC Participant Enrollment System.

4.6.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.6.3 Screen Failure, Registration, and Randomization

For candidates from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database.

Candidates who meet the enrollment criteria will be registered or randomized to the study according to standard ACTG DMC procedures.

4.7 Co-enrollment Guidelines

Sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Co-enrollment in A5128 does not require permission from the A5377 protocol chairs.

For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the core via actg.corea5377@fstrf.org and as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment for Arms A and C is defined as SAR441236 or placebo for SAR441236. Study treatment for Arm B is defined as SAR441236.

5.1 Regimens, Administration, and Duration

At entry, participants in Arms A and C **were** randomized 2:1 to receive blinded SAR441236 or placebo for SAR441236 and participants in Arm B will receive open-label SAR441236. The day of study treatment administration (either infusion or SC injection) (or first infusion, for Cohort 4) **was** Day 0. Cohorts 1 and 5 opened to accrual on the same day. Additional participants will be enrolled, 6 per cohort (or 12 for Cohort 4), into subsequent cohorts as these are opened to accrual. There is the possibility that an additional six participants could be enrolled into up to two Arm B cohorts. See section 10.4.2 for more information about this possibility.

Arm A (Double-Blinded)
Cohort 1A: (SAR441236)
SAR441236, 1 mg/kg in Sodium Chloride for Injection, 0.9% 50 mL, administered as a single intravenous (IV) infusion over 30 to 60 minutes on Day 0.

Cohort 1B: (placebo for SAR441236)
Sodium Chloride for Injection, 0.9% 50 mL, administered as a single IV infusion over 30 to 60 minutes on Day 0.

Cohort 2A: (SAR441236)
SAR441236, 3 mg/kg in Sodium Chloride for Injection, 0.9% 50 mL, administered as a single intravenous (IV) infusion over 30 to 60 minutes on Day 0.

Cohort 2B: (placebo for SAR441236)
Sodium Chloride for Injection, 0.9% 50 mL, administered as a single IV infusion over 30 to 60 minutes on Day 0.

Cohort 3A: (SAR441236)
SAR441236, 10 mg/kg in Sodium Chloride for Injection, 0.9% 250 mL, administered as a single intravenous (IV) infusion over 60 to 90 minutes on Day 0.
Cohort 3B: (placebo for SAR441236)
Sodium Chloride for Injection, 0.9% 250 mL, administered as a single IV infusion over 60 to 90 minutes on Day 0.

Cohort 4A: (SAR441236)
SAR441236, 30 mg/kg in Sodium Chloride for Injection, 0.9% 250 mL, administered as an intravenous (IV) infusion over 60 to 90 minutes on Day 0 and then every 12 weeks (at weeks 12, 24, and 36) for a total of four doses.

Cohort 4B: (placebo for SAR441236)
Sodium Chloride for Injection, 0.9% 250 mL, administered as an IV infusion over 60 to 90 minutes on Day 0 and then every 12 weeks (at weeks 12, 24, and 36) for a total of four doses.

Arm B (Open-Label)
Cohort 5:
SAR441236, 1 mg/kg, in Sodium Chloride for Injection, 0.9% 50 mL, administered as a single IV infusion over 30 to 60 minutes on Day 0.

Cohort 7 **(if opened)**:
SAR441236, 10 mg/kg, in Sodium Chloride for Injection, 0.9% 250 mL, administered as a single IV infusion over 60 to 90 minutes on Day 0.

Cohort 8:
SAR441236, 30 mg/kg, in Sodium Chloride for Injection, 0.9% 250 mL, administered as a single IV infusion over 60 to 90 minutes on Day 0.

Arm C (Double-Blinded)
Cohort 10A: (SAR441236)
SAR441236, 0.3 mg/kg, administered as a single subcutaneous (SC) injection on Day 0.

Cohort 10B: (placebo for SAR441236)
Sodium Chloride for Injection, 0.9%, administered as a single SC injection on Day 0.

Cohort 11A: (SAR441236)
SAR441236, 1 mg/kg, administered as a single SC injection or divided into multiple SC injections of a maximum of 2 mL per each syringe on Day 0.

Cohort 11B: (placebo for SAR441236)
Sodium Chloride for Injection, 0.9%, administered as a single SC injection or divided into multiple SC injections of a maximum of 2 mL per each syringe on Day 0.

Infusions
In Arms A and B, infusions of study treatment must be given over 30 to 60 minutes for 50 mL study IV bag or 60 to 90 minutes for 250 mL study IV bag. The entire volume in the study IV bag must be infused to the participant within the infusion time range as specified. However, the infusion rate may be slowed down to a minimal flow rate of 50 mL/hour or temporarily held in case unexpected events occur (e.g., acute infusion reactions, operational incident associated with treatment administration). The study treatment IV administration must be completed within 3 hours from the start of the infusion and within 16 hours from the date and time of study IV bag preparation.

The clinician responsible for administration and another study staff will each check the bag label and confirm that the participant identifier, weight (kg), cohort number, and calculated dose in mg based on participant's weight are correct.

An in-line filter infusion set must be used for IV administration. The main component of the fluid path of the infusion set must be polyethylene (PE) with a polyethersulfone (PES) in-line filter (0.2 micron). The pump segment of the fluid path of the administration set must be silicone or polyvinylchloride (PVC).

Prime the infusion set with Sodium Chloride for Injection, 0.9%, prior to study IV bag administration. At sites that cannot prime the line with Sodium Chloride for Injection, 0.9%, due to institutional requirements, the site may prime the line with study product solution from the participant's study IV bag.

When the entire volume of the study infusion bag has been emptied, sites must flush the line with Sodium Chloride for Injection, 0.9%, to ensure that any residual study product solution present in the drip chamber and the line is completely administered to the participant. The minimum amount (mL) of the flush will be determined by the maximum volume capacity of the administration set.

SC Injections

The study treatment SC administration should be completed within 15 minutes from the start of the injections and must be completed within 4 hours from the date and time of completion of syringe(s) preparation.

The clinician responsible for administration and another study staff member will each check the syringe label and confirm that the PID, weight (kg), cohort number, and calculated dose in mg based on participant's weight are correct.

Antiretroviral Therapy

Participants in Cohorts 1-4 and 10 and 11 will continue taking non-study-provided ART throughout the study.

Arm B participants **enrolled under Version 3.0** initiate**d** or re-initiate**d** combination ART (prescribed by their primary HIV clinician; not study-provided) on **or before** Day 28. **Arm B participants enrolled under Version 4.0 will initiate or re-initiate combination ART (prescribed by their primary HIV clinician; not study-provided) on Day 14.**

5.2 Study Product Formulation

The SAR441236 is supplied as a lyophilized sterile powder, containing L-histidine, L-histidine hydrochloride, sucrose, and polysorbate 80 as excipients, in a glass vial. Each vial contains 190 mg of SAR441236. The vials are intended for single use only. Two vials are packaged in each box. Vials must be stored refrigerated between 2°C and 8°C in an upright position in the box until use.

Sodium Chloride for Injection, 0.9%, in vials and in 50 mL and 250 mL IV bags are to be locally sourced by the site. The composition of the inner lining of the IV bag that is in contact with SAR441236 study product must be polyolefin (PO). Sodium Chloride for Injection, 0.9%, IV bags with the composition of the inner lining of the IV bag that is polyolefin (PO) must also be used to prepare Placebo for SAR441236 study IV bag to maintain blinding.

Sterile Water for Injection, preservative-free, single-use vials must be locally sourced by the site.

Syringes used for study product preparation and administration are to be locally sourced by the site. The composition of the inner lining of the syringe that is in contact with SAR441236 study product must be polypropylene (PP). To maintain the blind for Arm C participants, syringes with a PP inner lining must also be used in preparation of Placebo for SAR441236 for SC administration.

Needles are to be locally sourced by the site. The needles used for study product preparation must be luer lock between 18- and 21-gauge, stainless steel.

Needles used for study product SC administration must be luer lock, stainless steel. The needle gauge size and length used for SC administration is up to the site investigator's discretion.

The in-line filter is to be locally sourced by the site. The main component of the fluid path of the infusion set must be polyethylene (PE) with a polyethersulfone (PES) in-line filter (0.2 micron). The pump segment of the fluid path of the administration set must be silicone or PVC.

The IV pump used for the study IV infusion must be a volumetric infusion pump that can deliver infusion flow rates in the range of 50-250 mL/hour.

5.3 Study Product Preparation

The site pharmacist should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

The site pharmacist must be proficient in the preparation of study products using aseptic technique under a pharmacy Biological Safety Cabinet (BSC) Class II or better/isolator. Local regulations and site institutional policies and procedures for use of Personal Protective Equipment (PPE), such as gloves, gowns, masks, and safety glasses, must be followed.

Prescriptions

Prior to preparation of each study product in IV bag or syringe, a new written prescription must be sent to the pharmacy. The prescription must contain the participant's weight in kg based upon the most recent visit where weight was measured per the SOE, cohort number (1, 2, 3, 4, 5, 8, 10, or 11), and calculated SAR441236 dose (mg). 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's beginning preparation of study product.

The pharmacist must verify that the calculated dose (mg) written on the signed prescription received is correct based on the participant's weight (kg) and the mg/kg dose for the participant's assigned cohort number.

5.3.1 SAR441236, 1 mg/kg, and 3 mg/kg Dose Preparation in 50 mL IV Bag

Depending on the participant's SAR441236 dose (1 mg/kg or 3 mg/kg) and participant's weight (kg), one or two vials of SAR441236 will be needed to prepare a dose in IV bag.

Retrieve SAR441236 vial(s) from the refrigerator.

Reconstitute each vial of SAR441236 with 7.8 mL of Sterile Water for Injection (SWI) to yield SAR441236 solution concentration of 25 mg/mL in the vial. Use a 10 mL size luer lock syringe and luer lock, 18- to 21-gauge, stainless steel needle for reconstitution. The composition of the inner lining of the syringe that is in contact with SAR441236 study product must be polypropylene (PP).

With the vial placed upright on the counter inside of the BSC/isolator, insert the needle and transfer the SWI slowly directing the stream at the side of the vial containing the lyophilizate, making sure to recover any traces of powder on the inner walls of the vial.

Gently swirl the content of the vial in a circular motion for 20 seconds. Be sure to reconstitute any lyophilized powder that may be present on the inner wall and stopper of the vial while swirling. The vial should not be shaken or vigorously swirled.

Let the vial rest for a minimum of 20 minutes and up to 60 minutes to completely dissolve the content of the vial into a solution.

Gently swirl the content of the vial for 20 more seconds. The vial should not be shaken or vigorously swirled.

The reconstituted solution of SAR441236 at 25 mg/mL should be colorless to slightly yellow liquid that may contain white to off white particulates.

The resultant extractable volume per vial is 7.6 mL. Some air bubbles may still be present after 20 minutes, but all the lyophilized cake will be dissolved.

Withdraw the participant's calculated dose volume (mL) of SAR441236 from the reconstituted vial(s) into syringe(s). A separate syringe should be used to withdraw the solution per vial. Alternatively, various size luer lock syringes (up to 60 mL size syringe) may be used to withdraw the reconstituted solution from the vials into the syringe. If withdrawing from multiple vials, a new aspiration needle must be used to withdraw the reconstituted solution from each vial.

Retrieve a 50 mL Sodium Chloride for Injection, 0.9%, IV bag. The composition of the inner lining of the IV bag that is in contact with SAR441236 study product must be polyolefin (PO).

Withdraw equal volume (mL) of Sodium Chloride for Injection, 0.9%, from this bag that matches participant's calculated SAR441236 dose volume (mL) from this IV bag.

Inject the participant's calculated dose volume of SAR441236 into this Sodium Chloride for Injection, 0.9% IV bag to yield 50 mL total volume in this bag.

Label the participant's prepared study infusion bag as "SAR441236, ___mg or Placebo for SAR441236 in Sodium Chloride for Injection, 0.9% 50 mL total volume" for participants in Cohorts 1A, 1B, 2A, and 2B under Arm A (Blinded).

Label the participant's prepared study infusion bag as "SAR441236, ___ mg in Sodium Chloride for Injection, 0.9% 50 mL total volume" for participants in Cohorts 5, 6, and 9 under Arm B (Open-label).

The prepared study IV bag is stable for up to 16 hours at controlled room temperature between 20°C and 25°C. The prepared IV bag must be used, and the infusion completed within 16 hours from the end of IV bag preparation to the end of IV dose infusion.

Follow the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* manual and local regulations for preparing participant-specific study IV bag label.

Record the participant's calculated dose volume (mL) of reconstituted SAR441236 study product solution injected into the normal saline IV bag in the participant-specific pharmacy log.

5.3.2 SAR441236, 10 mg/kg and 30 mg/kg Dose Preparation in 250 mL IV Bag

Depending on the participant's SAR441236 dose (10 mg/kg or 30 mg/kg) and participant's weight (kg), up to 19 vials of SAR441236 will be needed to prepare a dose in IV bag.

Retrieve SAR441236 vials from the refrigerator.

Reconstitute each vial of SAR441236 with 7.8 mL of Sterile Water for Injection (SWI) to yield SAR441236 solution concentration of 25 mg/mL in the vial.

Use a 10 mL size luer lock syringe and luer lock, 18- to 21-gauge, stainless steel needle for reconstitution. The composition of the inner lining of the syringe that is in contact with SAR441236 study product must be polypropylene (PP).

With the vial placed upright on the counter inside of the BSC/isolator, insert the needle and transfer the SWI slowly directing the stream at the side of the vial containing the lyophilizate, making sure to recover any traces of powder on the inner walls of the vial.

Gently swirl the content of the vial in a circular motion for 20 seconds. Be sure to reconstitute any lyophilized powder that may be present on the inner wall and stopper of the vial while swirling. The vial should not be shaken or vigorously swirled.

Let the vial rest for a minimum of 20 minutes and up to 60 minutes to completely dissolve the content of the vial into a solution.

Gently swirl the content of the vial for 20 more seconds. The vial should not be shaken or vigorously swirled.

The reconstituted solution of SAR441236 at 25 mg/mL should be colorless to slightly yellow liquid that may contain white to off white particulates.

The resultant extractable volume per vial is 7.6 mL. Some air bubbles may still be present after 20 minutes, but all the lyophilized cake will be dissolved.

Withdraw the participant's calculated dose volume (mL) of SAR441236 from the reconstituted vials into syringe(s). A separate syringe should be used to withdraw the solution per vial. Alternatively, various size luer lock syringes (up to 60 mL size syringe) may be used to withdraw the reconstituted solution from the vials into the syringe. If withdrawing from multiple vials, a new aspiration needle must be used to withdraw the reconstituted solution from each vial.

Retrieve a 250 mL Sodium Chloride for Injection, 0.9%, IV bag. The composition of the inner lining of the IV bag that is in contact with SAR441236 study product must be polyolefin (PO).

Withdraw equal volume (mL) of Sodium Chloride for Injection, 0.9%, from this bag that matches participant's calculated SAR441236 dose volume (mL) from this IV bag.

Inject the participant's calculated dose volume of SAR441236 into this Sodium Chloride for Injection, 0.9%, IV bag to yield 250 mL total volume in this bag. Label the participant's prepared study infusion bag as "SAR441236, ___ mg or Placebo for SAR441236 in Sodium Chloride for Injection, 0.9%, 250 mL total volume" for IV bags prepared for participants in Cohorts 3A, 3B, 4A, and 4B under Arm A (Blinded).

Label the participant's prepared study infusion bag as "SAR441236, ___mg in Sodium Chloride for Injection, 0.9%, 250 mL total volume" for participants in Cohorts 7 and 8 under Arm B (Open-label).

The prepared study IV bag is stable for up to 16 hours at controlled room temperature between 20°C and 25°C. The prepared IV bag must be used, and the infusion completed within 16 hours from the end of IV bag preparation to the end of IV dose infusion.

Follow the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* manual and local regulations for preparing participant-specific study IV bag label.

Record the participant's calculated dose volume (mL) of reconstituted SAR441236 study product solution injected into the normal saline IV bag in the participant-specific pharmacy log.

5.3.3 Placebo for SAR441236, 1 mg/kg and 3 mg/kg Dose Preparation in 50 mL IV Bag

Retrieve a 50 mL Sodium Chloride for Injection, 0.9%, IV bag. To maintain blinding, the composition of the inner lining of the IV bag that is used must be polyolefin (PO).

Label the participant's prepared study infusion bag as "SAR441236, ___ mg or Placebo for SAR441236 in Sodium Chloride for Injection, 0.9%, 50 mL total volume" for IV bags prepared for participants in Cohorts 1A, 1B, 2A, and 2B under Arm A (Blinded).

The prepared study IV bag is stable for up to 16 hours at controlled room temperature between 20°C and 25°C. The prepared IV bag must be used, and the infusion completed within 16 hours from the end of IV bag preparation to the end of IV dose infusion.

Follow the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* manual and local regulations for preparing participant-specific study IV bag label.

5.3.4 Placebo for SAR441236, 10 mg/kg, or 30 mg/kg Dose Preparation in 250 mL IV Bag

Retrieve a 250 mL Sodium Chloride for Injection USP, 0.9%, IV bag. To maintain blinding, the composition of the inner lining of the IV bag that is used must be polyolefin (PO).

Label the participant's prepared study infusion bag as "SAR441236, ___ mg or Placebo for SAR441236 in Sodium Chloride for Injection USP, 0.9%, 250 mL total volume" for IV bags prepared for participants in Cohorts 3A, 3B, 4A, and 4B under Arm A (Blinded).

The prepared study IV bag is stable for up to 16 hours at controlled room temperature between 20°C and 25°C. The prepared IV bag must be used, and the infusion completed within 16 hours from the end of IV bag preparation to the end of IV dose infusion.

Follow the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* manual and local regulations for preparing participant-specific study IV bag label.

5.3.5 SAR441236, SC 0.3 mg/kg and 1 mg/kg Dose Preparation

Depending on the participant's SAR441236 dose (0.3 mg/kg or 1 mg/kg) and participant's weight (kg), one to three vials of SAR441236 will be needed to prepare an SC dose.

Retrieve SAR441236 vial(s) from the refrigerator.

Reconstitute each vial of SAR441236 with 7.8 mL of Sterile Water for Injection (SWI) to yield SAR441236 solution concentration of 25 mg/mL in the vial.

Use a 10 mL size luer lock syringe and luer lock, 18- to 21-gauge, stainless steel needle for reconstitution. The composition of the inner lining of the syringe that is in contact with SAR441236 study product must be polypropylene (PP).

With the vial placed upright on the counter inside of the BSC/isolator, insert the needle and transfer the SWI slowly, directing the stream at the side of the vial containing the lyophilizate, making sure to recover any traces of powder on the inner walls of the vial.

Gently swirl the contents of the vial in a circular motion for 20 seconds. Be sure to reconstitute any lyophilized powder that may be present on the inner wall and stopper of the vial while swirling. The vial should not be shaken or vigorously swirled.

Let the vial rest for a minimum of 20 minutes and up to 60 minutes to completely dissolve the contents of the vial into a solution.

Gently swirl the contents of the vial for 20 more seconds. The vial should not be shaken or vigorously swirled.

The reconstituted solution of SAR441236 at 25 mg/mL should be a colorless to slightly yellow liquid that may contain white to off-white particulates.

The resultant extractable volume per vial is 7.6 mL. Some air bubbles may still be present after 20 minutes, but all the lyophilized cake will be dissolved.

Withdraw the participant's calculated dose volume (mL) of SAR441236 from the reconstituted vials into 3mL size syringe(s). Each syringe can be filled with a maximum volume of 2 mL. One to three syringes may be prepared according to participant weight and calculated dose.

Use one vial for each syringe to be prepared. Any unused portion in the vial must be discarded.

Attach the appropriate needle for administration to the luer connection of the prepared SAR441236 study product in each of the syringe(s). Alternatively, the site pharmacist can attach a syringe cap to each of the prepared syringe(s). The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before SC administration.

The pharmacy and clinic staff are encouraged to work together to administer the dose specified in the protocol. When preparing the dose in a syringe and administering the dose, consideration should be given to the volume of liquid in the needle before and after the dose is administered. If the needle used to withdraw the product is replaced prior to study product administration, consideration should be given to conserving the full dose of the product.

One to three SC injections may be required depending on participant weight and calculated dose.

The SAR441236 study product solution in the syringe must be used within 4 hours at controlled room temperature between 20°C and 25°C (from the end of syringe preparation to the end of SC administration).

Record the time that SAR441236 reconstituted study product solution was withdrawn from the vial and into the syringe in the participant's pharmacy log. This is the time of preparation.

Label the participant's prepared study syringe(s) as "SAR441236, ___mg or Placebo for SAR441236" for participants in Cohorts 10A, 10B, 11A, and 11B under Arm C (Double-Blinded). If the participant's total calculated dose volume is withdrawn into multiple syringes, label each syringe # so the study staff is aware of the total number of syringes to administer to the study participant to administer the full dose. For example, if the participant's calculated total dose volume is withdrawn into two syringes, then label each syringe as either "syringe #1 of 2" or "syringe #2 of 2." Also include on the label the date and time of preparation and date and time of expiration. Follow the DAIDS Pharmacy Guidelines and local regulations for preparing participant-specific label(s).

5.3.6 Placebo for SAR441236, SC 0.3 mg/kg and 1 mg/kg Dose Preparation

Calculate the dose volume of reconstituted SAR441236 (25 mg/mL) depending on participant's assigned Cohort (Placebo for SAR441236, 0.3 mg/kg or Placebo for SAR441236, 1 mg/kg).

Retrieve Sodium Chloride for Injection, 0.9%, IV bag or vial(s).

Withdraw volume (mL) of Sodium Chloride for Injection, 0.9%, equal to the calculated dose volume of SAR441236 into 3 mL size luer lock syringe(s). Each syringe can be filled with a maximum volume of 2 mL. One to three syringes may be prepared according to participant weight and calculated dose.

Attach the appropriate needle for administration to the luer connection of the prepared SAR441236 study product in each of the syringe(s). Alternatively, the site pharmacist can attach a syringe cap to each of the prepared syringe(s). The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before SC administration.

The pharmacy and clinic staff are encouraged to work together to administer the dose specified in the protocol. When preparing the dose in a syringe and administering the dose, consideration should be given to the volume of liquid in the needle before and after the dose is administered. If the needle used to withdraw the product is replaced prior to study product administration, consideration should be given to conserving the full dose of the product.

One to three SC injections may be required depending on participant weight and calculated dose.

The Placebo for SAR441236 (Sodium Chloride for Injection, 0.9%) in the syringe should be used within 4 hours at controlled room temperature between 20°C and 25°C (from the end of syringe preparation to the end of SC administration).

Record the time that SAR441236 reconstituted study product solution was withdrawn from the vial and into the syringe in the participant's pharmacy log. This is the time of preparation.

Label the participant's prepared study syringe(s) as "SAR441236, ___mg or Placebo for SAR441236" for participants in Cohorts 10A, 10B, 11A, and 11B under Arm C (Double-Blinded). If the participant's total calculated dose volume is withdrawn into multiple syringes, label each syringe # so the study staff is aware of the total number of syringes to administer to the study participant to administer the full dose. For example, if the participant's calculated total dose volume is withdrawn into two syringes, then label each syringe as either "syringe #1 of 2" or "syringe #2 of 2." Also include on the label the date and time of preparation and date and time of expiration. Follow the DAIDS Pharmacy Guidelines and local regulations for preparing participant-specific label(s).

5.4 Pharmacy: Product Supply, Distribution, and Accountability

5.4.1 Study Product Acquisition/Distribution

SAR441236 will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product for this protocol

by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.4.2 Study Product Accountability

The ACTG site pharmacist is required to maintain complete records of SAR441236 study product received from the NIAID CRPMC and subsequently dispensed. As the Sodium Chloride for Injection, 0.9% and Sterile Water for Injection will be obtained locally by the site, the continuous inventory is not required but all other information must be completed (including the manufacturer and lot number of the vial and IV solution used. All unused study product must be returned to the NIAID CRPMC after the study is completed or terminated. The procedures to be followed are in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section entitled, "Study Product Management Responsibilities."

5.5 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at https://www.ppmdb.org/PPMD.

5.5.1 Required Medications

All participants in Arm A and Arm C are required to take their current ART regimen until study completion. **Beginning with Version 4.0,** participants in Arm B should initiate or re-initiate a combination ART regimen beginning on Day **14**. The core team should be advised via actg.corea5377@fstrf.org of any participants who develop a toxicity related to a component of their ART in advance of ART modification, if possible. See toxicity management guidelines in section 8.0.

5.5.2 Prohibited Medications

Antiretroviral agents
Use of any of the following is prohibited prior to study entry, at entry, and at any time during the study:

- Maraviroc
- Ibalizumab
- Enfuvirtide

Participants may receive vaccines as outlined below:

Standard vaccines, **other than** influenza (i.e., **"**flu**"**) **or SARS-CoV-2 (i.e., COVID-19) vaccines**, **are NOT permitted** within 30 days **before or after study drug administration**.

Flu vaccines and/or SARS-CoV-2 vaccines granted Emergency Use Authorization (EUA) will be permitted within 30 days before or after receiving study drug, but must be approved in advance by the study's core team (actg.corea5377@fstrf.org).

All FDA-approved and SARS-CoV-2 vaccines that have been granted EUA will be permitted more than 30 days before or after study drug administration.

Other biological products (biologics), either approved or investigational, are prohibited.

5.5.3 Precautionary Medications

None.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1-1: SOE for Arm A Cohorts 1-3

Evaluation (Arm A, Cohorts 1-3)	Screening	Pre-Entry	Entry (Day 0; *see section 6.2.2*)	Post-infusion Evaluations									Prem. Tx or Study Discontinuation (D/C)
				D.1	D.2	D.3	Wk. 1	Wk. 2	Wk. 4	Wk. 8	Wk. 12	Wk. 24	
Visit Window→	*-45 days*	*At least 24 hr before Entry*		*As indicated*			*±1 day*	*±2 days*		*±7 days*			
Documentation of HIV	X												
Medical history	X		X										
Medication history	X		X										
Clinical assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X								X			X
Hematology, Chemistries, & liver function tests (LFTs)	X		X		X		X	X		X			X
Fasting lipids	X												
Hepatitis screen	X												
hsCRP			X										
Urinalysis			X					X			X		X

Evaluation (Arm A, Cohorts 1-3)	Screening	Pre-Entry	Entry (Day 0; *see section 6.2.2*)	Post-infusion Evaluations									Prem. Tx or Study Discontinuation (D/C)
				D.1	D.2	D.3	Wk. 1	Wk. 2	Wk. 4	Wk. 8	Wk. 12	Wk. 24	
Visit Window→	*-45 days*	*At least 24 hr before Entry*		*As indicated*			*±1 day*	*±2 days*		*±7 days*			
Pregnancy testing	X		X	As indicated									X
$CD4^+/CD8^+$	X		X					X			X	X	X
Stored plasma/PBMC		X	X					X	X	X	X	X	X
Stored serum			X					X	X	X	X	X	X
Viral reservoir assays		X	X						X	X	X	X	
Plasma HIV-1 RNA SCA		X	X						X	X	X	X	
Anti-drug antibodies (ADA)			X					X	X		X	X	X
Plasma HIV-1 RNA	X		See Table 6.1-2, below					X			X	X	X
Infusion (SAR441236 or placebo)													
Pharmacokinetic (PK) blood collection			See Table 6.1-2 below										

Table 6.1-2: Infusion/PK/HIV-1 RNA Timing SOE for Arm A Cohorts 1-3

Infusion/PK/ HIV-1 RNA-related Evaluation (Arm A Cohorts 1-3)	Day 0 (Day of Infusion) Pre-infusion, Infusion, , and Immediately Post-infusion			Hours (Day/s) Post-infusion *(all times are relative to Hour 0)*							Weeks Post-infusion						
	Before infusion begins	Infusion	Hour 0 (when infusion ends)	+2 hr	+4 hr	+6 hr	+10 hr	+24 hr (Day 1)	+48 hr (Day 2)	+72 hr (Day 3)	Wk.1	Wk. 2	Wk. 4	Wk. 8	Wk. 12	Wk. 24	Prem. Tx or Study D/C
Visit Window →			*+0 to 15 min*	*±15 min*				*±4 hr*	*±8 hr*	*±12 hr*	*±1 day*	*±2 days*		*±7 days*			
Plasma HIV-1 RNA	X											See Table 6.1-1					
Infusion (SAR441236 or placebo)		X															
Vital signs and targeted symptom assessment	X	X	X	X	X	X	X	X	X	X	X	X					
PK blood collection	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 6.1-3: Arm A, Cohort 4, Infusion #1

Evaluation (Arm A, Cohort 4, Infusion #1)	Screening	Pre-Entry	Entry (D. 0; *see section 6.2.2*)	Post-infusion Evaluations							Prem. Tx or Study Discontinuation (D/C)
				D.1	D.2	D.3	Wk. 1	Wk. 2	Wk. 4	Wk. 10 **(and 2 wks before Infusion #2)**	
Visit Window →	*-45 days*	*At least 24 hr before Entry*		*As indicated*			*±1 day*	*±2 days*		*±7 days*	
Documentation of HIV	X										
Medical History	X		X								
Medication History	X		X								
Clinical assessments	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X				X	X		X	X
Hematology, Chemistries, & LFTs	X		X		X		X	X		X	X
Fasting lipids	X										
Hepatitis screen	X										
hsCRP			X								
Urinalysis			X					X			X

Evaluation (Arm A, Cohort 4, Infusion #1)	Screening	Pre-Entry	Entry (D. 0; *see section 6.2.2*)	Post-infusion Evaluations							Prem. Tx or Study Discontinuation (D/C)
				D.1	D.2	D.3	Wk. 1	Wk. 2	Wk. 4	Wk. 10 **(and 2 wks before Infusion #2)**	
Visit Window →	*-45 days*	*At least 24 hr before Entry*		*As indicated*			*±1 day*	*±2 days*		*±7 days*	
Pregnancy testing	X		X	As indicated							X
$CD4^+/CD8^+$	X		X					X			X
Stored plasma/PBMC		X	X					X	X	X	X
Stored serum			X					X	X	X	X
Viral reservoir assays		X	X						X		
Plasma HIV-1 RNA SCA		X	X						X		
Anti-drug antibodies (ADA)			X					X	X		X
Plasma HIV-1 RNA	X		See Table 6.1-4 below					X			X
Infusion #1 (SAR441236 or placebo)											
PK blood collection			See Table 6.1-4 below								

Table 6.1-4: Infusion/PK/HIV-1 RNA Timing SOE for Arm A, Cohort 4, Infusion #1

Infusion/PK/HIV-1 RNA-related Evaluation (Arm A, Cohort 4, Infusion #1)	Day 0 (Day of Infusion) Pre-infusion, Infusion, and immediately Post-infusion			Hours (Day/s) Post-infusion *(all times are relative to Hour 0)*							Weeks Post-infusion				
	Before infusion begins	Infusion	Hour 0 (when infusion ends)	+2 hr	+4 hr	+6 hr	+10 hr	+24 hr (Day 1)	+48 hr (Day 2)	+72 hr (Day 3)	Wk. 1	Wk. 2	Wk. 4	Wk. 10 **(and 2 wks before Infusion #2)**	Prem. Tx or Study D/C
Visit Window →			*+0 to 15 min*	*±15 min*				*±4 hr*	*±8 hr*	*±12 hr*	*±1 day*	*±2 days*		*±7 days*	
HIV-1 RNA	X											See Table 6.1-3			
Infusion (SAR441236 or placebo)		X													
Vital signs and targeted symptom assessment	X	X	X	X	X	X	X	X	X	X	X	X			
PK blood collection	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 6.1-5: Arm A, Cohort 4, Infusion #2

Evaluation Cohort 4, Infusion #2	R (Infusion **#2** Day)				Post-infusion **#2** Day Evaluations						Prem. Tx or Study D/C
	Before infusion begins	Infusion	Hour 0 (when infusion ends)	2 hours after Hour 0	+1 Day (telephone ok)	+2 Days	**R+ 1** Wk.	**R + 2** Wk.	**R+ 4** Wk.	**R+ 10** Wk. **(and 2 wks before Infusion #3)**	
Visit Window →	*±1 week*				*As indicated*		*±1 day*	*±2 days*		*±7 days*	
Clinical assessments	X					X	X	X	X	X	X
Weight	X					X	X	X		X	X
Hematology, Chemistries, & LFTs	X					X	X	X		X	X
Urinalysis	X							X			X
Pregnancy testing	X				As indicated						X
$CD4^+/CD8^+$	X										X
Stored plasma/PBMC	X								X	X	X
Stored serum	X								X	X	X
Viral reservoir assays	X										
Plasma HIV-1 RNA SCA	X										
Anti-drug antibodies (ADA)	X										X

Evaluation Cohort 4, Infusion #2	R (Infusion **#2** Day)				Post-infusion **#2** Day Evaluations						Prem. Tx or Study D/C
	Before infusion begins	Infusion	Hour 0 (when infusion ends)	2 hours after Hour 0	+1 Day (telephone ok)	+2 Days	**R+ 1** Wk.	**R + 2** Wk.	**R+ 4** Wk.	**R+ 10** Wk. **(and 2 wks before Infusion #3)**	
Visit Window →	*±1 week*				*As indicated*		*±1 day*	*±2 days*		*±7 days*	
HIV-1 RNA	X										X
Infusion (SAR441236 or placebo)		X									
Vital signs	X	X	X	X			X				
Targeted symptom assessment	X	X	X	X	X		X	X	X		
PK blood collection	X						X	X	X	X	X

Table 6.1-6: Arm A, Cohort 4, Infusion #3

Evaluation Cohort 4, Infusion #3	**R** (Infusion **#3** Day)				Post-infusion **#3** Day Evaluations						Prem. Tx or Study D/C
	Before infusion begins	Infusion	Hour 0 (when infusion ends)	2 hours after Hour 0	+1 Day (telephone ok)	+2 Days	**R+ 1** Wk.	**R+ 2** Wk.	**R+ 4** Wk.	**R+ 10** Wk. **(and 2 wk <Inf. #4)**	
Visit Window →	*±1 week*				*As indicated*		*±1 day*	*±2 days*		*±7 days*	
Clinical assessments	X					X	X	X	X	X	X
Weight	X					X	X	X		X	X
Hematology, Chemistries, & LFTs	X					X	X	X		X	X
Urinalysis	X							X			X
Pregnancy testing	X				As indicated						X
$CD4^+/CD8^+$	X										X
Stored plasma/PBMC	X								X	X	X
Stored serum	X								X	X	X
Viral reservoir assays	X										
Plasma HIV-1 RNA SCA	X										
Anti-drug antibodies (ADA)	X										X
HIV-1 RNA	X										X

Evaluation Cohort 4, Infusion #3	**R** (Infusion **#3** Day)				Post-infusion **#3** Day Evaluations						Prem. Tx or Study D/C
	Before infusion begins	Infusion	Hour 0 (when infusion ends)	2 hours after Hour 0	+1 Day (telephone ok)	+2 Days	**R+ 1** Wk.	**R+ 2** Wk.	**R+ 4** Wk.	**R+ 10** Wk. **(and 2 wk <Inf. #4)**	
Visit Window →	*±1 week*				*As indicated*		*±1 day*	*±2 days*		*±7 days*	
Infusion (SAR441236 or placebo)		X									
Vital signs	X	X	X	X		X					
Targeted symptom assessment	X	X	X	X	X	X	X	X			
PK blood collection	X					X	X	X	X	X	X

Table 6.1-7: Arm A Cohort 4, Infusion #4 through study end

Evaluation	**R #4** (Infusion Day)	Post-infusion **#4** Evaluations							Prem. Tx or Study D/C
		Infusion **#4** +2 Days	**R+ 1** Wk.	**R+ 2** Wk.	**R+ 4** Wk.	**R+ 12** Wk.	**R+ 24** Wk.	**R+ 36** Wk.	
Visit Window →	*±1 week*	*As indicated*	*±1 day*	*±2 days*		*±7 days*			
Clinical assessments	X	X	X	X	X	X	X	X	X
Weight	X		X	X		X			X
Hematology, Chemistries, & LFTs	X	X	X	X		X			X
Urinalysis	X			X					X
Pregnancy testing	X	As indicated							X
$CD4^+/CD8^+$	X					X		X	X
Stored plasma/PBMC	X				X	X	X	X	X
Stored serum	X			X	X	X	X	X	X
Viral reservoir assays	X					X		X	
Plasma HIV-1 RNA SCA	X					X		X	
Anti-drug antibodies (ADA)	X					X		X	X
HIV-1 RNA	See Table 6.1-8 below					X		X	X
Infusion (SAR441236 or placebo)									
PK blood collection	See Table 6.1-8 below								

Table 6.1-8: Infusion/PK/HIV-1 RNA Timing SOE for Arm A, Cohort 4, Infusion #4

Infusion/PK/HIV-1 RNA-related Evaluation (Arm A, Cohort 4, Infusion #4)	**R** (Day of **#4** Infusion) Pre-infusion, Infusion, and Immediately Post-infusion			Hours (Day/s) Post-infusion **#4** *(all times are relative to Hour 0)*						Weeks Post-infusion						
	Before infusion begins	Infusion	Hour 0 (when infusion ends)	+2 hr	+4 hr	+6 hr	+10 hr	+ 24 hr (+1 Day)	+ 48 hr (+2 Days)	**R+ 1** Wk.	**R+ 2** Wk.	**R+ 4** Wk.	**R+ 12** Wk.	**R+ 24** Wk.	**R+ 36** Wk.	Prem. Tx or Study D/C
Visit Window →		*± 1 wk.*	*+0 to 15 min*	*±15 min*				*±4 hr*	*±8 hr*	*±1 day*	*±2 days*		*±7 days*			
Plasma HIV-1 RNA	X										See Table 6.1-7					
Infusion (SAR441236 or placebo)		X														
Vital signs and targeted symptom assessment	X	X	X	X	X	X	X	X	X	X	X					
PK blood collection	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 6.1-9: Arm B Cohorts

Evaluation (Arm B, all cohorts)	Screening	Entry (Day 0; see section 6.2.2 for timing)	Post-infusion **Visits**												Prem. Tx/ or Study D/C
			D.1	D.2	D.3	D.4	D.7	D.10	Wk. 2	Wk. 3	Wk. 4	Wk. 8	Wk. 12	Wk. 24	
Visit Window →	*-45 days*		*As indicated*				*±1 day*		*±2 days*			*±7 days*			
Documentation of HIV	X														
Medical history	X														
Medication history **(see section 6.3.2)**	X														
Clinical assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X		X		X	X			X
Hematology, Chemistries, & LFTs	X	X		X			X		X		X	X			X
Fasting lipids		**X**													
Hepatitis screen		**X**													
hsCRP		X													
Urinalysis		X							X				X		X
Pregnancy testing	X	X	As indicated												X

Evaluation (Arm B, all cohorts)	Screening	Entry (Day 0; see section 6.2.2 for timing)	Post-infusion **Visits**												Prem. Tx/ or Study D/C
			D.1	D.2	D.3	D.4	D.7	D.10	Wk. 2	Wk. 3	Wk. 4	Wk. 8	Wk. 12	Wk. 24	
Visit Window →	*-45 days*		*As indicated*				*±1 day*		*±2 days*			*±7 days*			
$CD4^+/CD8^+$		X							X				X	X	X
Stored plasma/PBMC		X					X		X		X	X	X	X	X
Stored serum		X					X		X		X	X	X	X	X
Phenotypic HIV-1 susceptibility testing		X									X				
Anti-drug antibodies (ADA)		X							X		X		X	X	X
HIV-1 RNA	**See sections 4.2.10 & 4.2.11**	See Table 6.1-10	X	X	X	X	X	X	**X**	X	X	X	X	X	X
Infusion															
PK blood collection		See Table 6.1-10 below													
ART initiation or re-initiation									**X**						

Table 6.1-10: Infusion/PK/HIV-1 RNA Timing SOE for Arm B, All Cohorts

Infusion/PK/HIV-1 RNA-related Evaluation (Arm B)	Day 0 (Day of Infusion) Pre-infusion, Infusion, and Immediately Post-infusion			Hours (Day/s) Post-infusion *(all times are relative to Hour 0)*								Days/Weeks Post-infusion								
	Before infusion begins	Infusion	Hour 0 (when infusion ends)	+2 hr	+4 hr	+6 hr	+10 hr	+24 hr (Day 1)	+48 hr (Day 2)	+72 hr (Day 3)	+96 hr (Day 4)	Day 7	Day 10	Wk. 2	Wk. 3	Wk. 4	Wk. 8	Wk. 12	Wk. 24	Prem. Study or Tx D/C
Visit Window →			*+0 to 15 min*	*±15 min*				*±4 hr*	*±8 hr*	*±12 hr*		*±1 day*		*±2 days*			*±7 days*			
Infusion (SAR441236)		X												See Table 6.1-9						
Vital signs and targeted symptom assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Intensive HIV-1 RNA, Day 0 only	X		X	X	X	X	X													
PK blood collection	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 6.1-11: SOE for Arm C Cohorts 10 and 11

Evaluation (Arm C Cohorts 10-11)	Screening	Pre-Entry	Entry (Day 0; *see section 6.2.2*)	Post-SC Injection Evaluations									Prem. Tx or Study Discontinuation (D/C)
				D.1	D.2	D.3	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 24	
Visit Window→	*-45 days*	*At least 24 hr before Entry*		*As indicated*			*±1 day*	*±2 days*		*±7 days*			
Documentation of HIV	X												
Medical history	X		X										
Medication history	X		X										
Clinical assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X				X	X		X			X
Hematology, Chemistries, & liver function tests (LFTs)	X		X		X		X	X		X			X
Fasting lipids	X												
Hepatitis screen	X												
hsCRP			X										
Urinalysis			X					X			X		X
Pregnancy testing	X		X	As indicated									X
$CD4^+/CD8^+$	X		X					X			X	X	X

Evaluation (Arm C Cohorts 10-11)	Screening	Pre-Entry	Entry (Day 0; *see section 6.2.2*)	Post-SC Injection Evaluations									Prem. Tx or Study Discontinuation (D/C)
				D.1	D.2	D.3	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 24	
Visit Window→	*-45 days*	*At least 24 hr before Entry*		*As indicated*			*±1 day*	*±2 days*		*±7 days*			
Stored plasma/PBMC		X	X					X	X	X	X	X	X
Stored serum			X					X	X	X	X	X	X
Viral reservoir assays		X	X						X	X	X	X	
Plasma HIV-1 RNA SCA		X	X						X	X	X	X	
Anti-drug antibodies (ADA)			X					X	X		X	X	X
Plasma HIV-1 RNA	X		See Table 6.1-12, below					X			X	X	X
SC Injection (SAR441236 or placebo)													
PK blood collection			See Table 6.1-12 below										

Table 6.1-12: SC Injection/PK/HIV-1 RNA Timing SOE for Arm C Cohorts 10-11

SC Injection/PK/ HIV-1 RNA-related Evaluation (Arm C Cohorts 10-11)	Day 0 (Day of SC Injection) Pre-SC Injection, SC Injection, and Immediately Post-SC Injection			Hours (Day/s) Post-SC Injection *(all times are relative to Hour 0)*							Weeks Post-SC injection						
	Before SC injection begins	SC injection	Hour 0 (when SC injection ends)	+2 hr	+4 hr	+6 hr	+10 hr	+24 hr (Day 1)	+48 hr (Day 2)	+72 hr (Day 3)	Wk.1	Wk. 2	Wk. 4	Wk. 8	Wk. 12	Wk. 24	Prem. Tx or Study D/C
Visit Window →			*+0 to 15 min*	*±15 min*				*±4 hr*	*±8 hr*	*±12 hr*	*±1 day*	*±2 days*		*±7 days*			
Plasma HIV-1 RNA	X											See Table 6.1-11					
SC injection (SAR441236 or placebo)		X															
Vital signs and targeted symptom assessment	X		X	X	X	X	X	X	X	X	X	X					
PK blood collection	X		X				X	X	X	X	X	X	X	X	X	X	X

6.2 Timing of Evaluations

6.2.1 Screening and Pre-Entry Evaluations

Screening and pre-entry evaluations must occur prior to the participant's starting any study medications, treatments, or interventions.

Screening
Screening evaluations to determine eligibility must be completed within 45 days prior to study entry except as otherwise specified. **For Arm B candidates, completion of screening within 5 days prior to entry is encouraged.**

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on candidates who do not enroll will be captured in a Screening Failure Results form and entered into the ACTG database.

Pre-Entry (Arms A and C only)
Pre-entry evaluations must be completed after screening evaluation results demonstrating a candidate's eligibility for the study are available and at least 24 hours prior to entry.

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after pre-entry evaluations for Arms A and C. **For Arm B, entry evaluations may occur on the same day as screening evaluations but must begin only after eligibility is confirmed based on results from screening evaluations.** Participants must begin treatment within 3 days after randomization or registration.

Sites are required to use the scheduling utility (found on the DMC website: www.fstrf.org) to schedule each participant's entry visit and treatment administration date. Sites are also required to use the scheduling utility to schedule each Cohort 4 participant's subsequent infusions.

NOTE: With the exception of post-dosing collections for PK studies (see section 11.0), blood collections and other evaluations that are scheduled for the day of treatment administration must be completed before the administration begins.

6.2.3 Post-Entry Evaluations

The visit schedules in the schedules of evaluation (SOE) must be based on the day of the administration (i.e., the day of infusion or SC injection = Day 0).

NOTE: For participants in Cohort 4, with the exception of post-dosing collections for PK studies (see section 11.0), blood collections and other evaluations

that are scheduled for the days of infusion must be completed before the infusion begins.

Except as noted below, if a participant is outside of a defined post-entry visit window, the site must notify the core team within 24 hours at: actg.corea5377@fstrf.org.

Remote Data Collection – All Cohorts
Study visits may be conducted remotely (e.g., telephone, telehealth) in the following situations:

- A participant is unable to attend a visit **(e.g.,** because of illness**, because of concern about exposure to illness)**; the site must inform the core team (actg.corea5377@fstrf.org)
- The site is temporarily unable to conduct non-essential visits in the clinic; the site must inform the core team (actg.corea5377@fstrf.org)
- At the discretion of the A5377 team; a message from the team will be sent to all sites.

Regardless of the situation, sites should document which visits were conducted remotely and attempt to obtain as much as possible of the visit-specific required information based on the SOE and record it. The impacted visits and rationale must be reported and documented following instructions provided by the team or network leadership. In general, and unless otherwise instructed by the team, participants should not be discontinued from the study via a remote visit.

Unanticipated Interruptions in Cohort 4 Dosing Schedule
If, after a Cohort 4 participant has undergone at least one infusion it is not possible to follow the current and subsequent SOEs for any reason, sites must notify the study's core team (actg.corea5377@fstrf.org) to receive instructions for a modified follow-up schedule.

In general, sites should attempt to conduct all safety evaluations through 4 weeks post-latest infusion, after which they should follow the single-dose infusion SOE Table 6.1-1, beginning at the week that corresponds to the participant's post-infusion time point. These visits may be conducted remotely. No participants should be discontinued from the study without the sites' having received permission to do so from the study team. Sites should use their best judgment regarding maintaining telephone or other contact with participants after the Table 6.1-1 week 24 visit.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized or Registered Participants Who Do Not Start Study Treatment
All eCRFs must be keyed for the period up to and including the entry visit. No further evaluations are required. Participants who do not start study treatment will be replaced.

Premature Treatment Discontinuation Evaluations
Except for participants in Arm A Cohort 4, participants who do not receive at least 90% of their intended dose **should remain on study and be followed according to their SOE for 12 weeks after the infusion. Participants in** Cohort 4 who **receive only a single infusion (i.e., for whom a decision not to continue with infusions is reached before the second infusion is scheduled) should remain on study and be followed per SOE Table 6.1-1 through week 24. Participants in Cohort 4 who receive at least two infusions (or parts thereof) but who** will not complete all four infusions, should remain on study and be followed per SOE **Table 6.1-7** for **36** weeks following their last infusion.

Participants who are unwilling/unable to remain on study for the entire follow-up period **described above** will complete the premature treatment/study evaluations and be taken off study.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue study participation after receiving the full dose, or, in the case of participants in Cohort 4, prior to the completion of all infusions, **of study treatment** should be encouraged to stay on study and be followed per the SOE for at least 12 weeks following the last receipt of study treatment. **This follow-up guidance applies to participants who are replaced following receipt of at least one dose of study treatment.** At their final visit, **participants** will have the premature study discontinuation evaluations performed per the SOE and will be taken off study.

Discontinuation During Remote Data Collection
Unless otherwise instructed by the study team, sites should not discontinue participants via a remote visit. During the time that sites must conduct scheduled study visits remotely, participants who reach their final scheduled visit should be retained on study until all required evaluations and blood collections can be performed. Sites should use their best judgment regarding maintaining telephone or other contact with participants until the final study visit can be conducted in person.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: **https://www.niaid.nih.gov/sites/default/files/score-source-documentation-requirements.pdf**.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the DAIDS AE Grading Table and AE reporting of adverse events requirements.

The protocol team and/or study monitoring entity may determine after the protocol or amendment has been finalized that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.2 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 30 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures within the previous 5 years (oral history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- Autoimmune disease

Any allergies to any medications and their formulations must also be documented.

For Arm B, the medical history may be collected at screening and/or entry but must be completed in advance of SAR441236 infusion.

6.3.3 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history. **For Arm B, the medication history may be collected at screening and/or entry but must be completed in advance of SAR441236 infusion.**

Table 6.3.3-1: Medication History

Medication Category	Timeframe
Antiretroviral therapy	Complete history
Immune-based therapy	Within 1 year prior to entry
Blinded study treatment	Within 1 year prior to entry
HIV-1-related vaccines	Complete history
Other vaccines, including COVID-19	**Within 1 year prior to entry**
HIV-1 latency reversal agents	Complete history
Prescription drugs	Within 30 days prior to entry
Nonprescription drugs	Within 30 days prior to entry
Alternative therapies	Within 30 days prior to entry
Dietary supplements	Within 30 days prior to entry
Sex-hormone medications or sex-hormone analogues or antagonists*	Within 1 year prior to entry except as noted below

*Includes: Hormone-releasing IUDs (e.g., Mirena inserted in the last 5 years); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors or any other androgen, estrogen, or progesterone analogue or antagonist therapy.

6.3.4 Clinical Assessments

Complete Physical Examination
A complete physical examination is to be performed at screening and is to include, at a minimum, an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac examination; abdominal examination; and examination of the lower extremities for edema. The complete physical examination will also include signs and symptoms, diagnoses, and vital signs (i.e., temperature, pulse, respiration rate, and blood pressure) plus height.

Weight
Weight will be measured and recorded as indicated on the SOE.

Targeted Physical Examination
A targeted physical examination is to be conducted at pre-entry for Arm A and Arm C candidates and at all on-study visits for all participants in both arms. The examination is to include vital signs and is to be driven by any previously identified or new adverse event/targeted event that the participant has experienced since the last visit or at this visit. See section 8.3 for post-entry pregnancy recording requirements.

Concomitant Medications
Post-entry, record all concomitant medications, including ART.

Study Treatment Modifications
Record all study treatment modifications, including initial dose, and any participant-initiated and/or protocol-mandated modifications. Record any permanent discontinuation of treatment.

Vaccinations
See section 5.5.2 for information about restrictions on vaccinations.

6.3.5 Laboratory Evaluations

Each study site and laboratory involved in this study must comply with the DAIDS policy on Requirements for Laboratories Performing Testing for DAIDS-Supported and/or Sponsored Clinical Trials, which is available at: https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf.

At screening, pre-entry, and entry, all laboratory values must be recorded. For post-entry assessments, record all creatinine, AST/ALT, and white blood cell count (WBC) **and differentials**.

On the day of and for 2 weeks after any SAR441236/placebo administration, all of the following must be recorded and keyed within 2 business days:

- Creatinine
- AST/ALT
- WBC **and differentials**
- Any abnormal (Grade ≥1) laboratory findings per section 7.2

Hematology
Hemoglobin, hematocrit, WBC, WBC differential, absolute neutrophil count (ANC), platelets.

Blood chemistries
Creatinine, blood urea nitrogen (BUN), uric acid, total protein, albumin, glucose, calculated creatinine clearance estimated by the Cockcroft-Gault equation, electrolytes (sodium, potassium, chloride, and CO_2/bicarbonate).

Refer to the calculator located on the FSTRF website: Calculated Creatinine Clearance - Cockcroft-Gault Equation (Adult). **Creatinine clearance must be graded using the categorical mL/min values from the DAIDS AE Grading Table. The percent change criteria does not apply.**

Liver function tests (LFTs)
Total bilirubin, AST [SGOT], ALT [SGPT], alkaline phosphatase.

Fasting Lipids
Total cholesterol, LDL and HDL cholesterol, triglycerides **will be measured in a**

fasted state according to the SOE. Participants should fast for at least 8 hours prior to **this** visit. Fasting is defined as nothing to eat or drink other than water and required medications. Fasting state will be recorded as yes/no. If a participant arrives for the visit and is not fasting, the visit will proceed; no re-scheduling is required.

Hepatitis Screening
Hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibody testing will be done per the SOE. HCV RNA testing is required if HCV antibody positive.

hs-CRP
At entry only, high-sensitivity C-reactive protein.

Urinalysis
Blood, glucose, leukocyte esterase, pH, and protein. A microscopic urinalysis is only necessary if the dipstick result is abnormal.

Pregnancy Test
For **participants of** reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of <25 mIU/mL.) Record pregnancy and pregnancy outcome per section 8.0.

6.3.6 Immunologic Studies

The current LPC provides instructions for processing, storing, and shipping the samples described below.

$CD4^+/CD8^+$
At screening, **when indicated in the SOE,** obtain absolute $CD4^+/CD8^+$ count and percentages from a US laboratory that possesses a CLIA certification or equivalent.

For entry and post-entry evaluations, all laboratories must possess a CLIA certification or equivalent.

Anti-drug antibodies (ADA)
Plasma for ADA levels will be collected as indicated in the SOE.

6.3.7 Virologic Studies

The current LPC provides instructions for processing, storing, and shipping the samples described below.

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed using any FDA-approved assay at a laboratory that possesses a CLIA certification or equivalent. On-study plasma HIV-1 RNA must be performed using the FDA-approved assay and at the

laboratory indicated in the current LPC **or at a laboratory that has CLIA certification or equivalent and is certified by the DAIDS Virology Quality Assurance (VQA) Program**.

In Arm B, on the day of infusion, blood will be collected multiple times for plasma HIV-1 RNA testing as indicated in SOE Table 6.1-10.

Stored Plasma/PBMC
Blood for stored samples of plasma and PBMCs will be collected from all participants as indicated in the SOEs.

Stored Serum
Blood for stored samples of serum will be collected from all participants as indicated in the SOEs.

Viral Reservoir Assays
For participants in Arm A, PBMC for viral reservoir assays (e.g., cell-associated HIV-1 RNA [caRNA] and proviral DNA) will be obtained as indicated in the SOE.

Plasma HIV-1 RNA Single Copy Assay (SCA)
Plasma for HIV-1 RNA determination by SCA will be collected from participants in Arm A as indicated in the SOE.

Phenotypic HIV-1 Susceptibility Testing
Plasma for HIV-1 susceptibility testing will be collected from Arm B participants as indicated in the SOE.

6.3.8 Infusion

On the days indicated in the SOEs, study treatment will be administered by IV infusion according to instructions provided in sections 5.1 and 5.3.

Record and key the following within 2 business days after study treatment administration: dose administered, rate of infusion, whether the full dose was administered, the start and stop times of all infusions, and will note the start and stop time of, and reason for, any interruption or change in the rate of infusion. Except in the case of infusion site reactions, infusions should be completed even if doing so exceeds the expected duration of the infusion, depending on the dose (see section 5.3). The time of the completion of the infusion will be known as Hour 0 for all participants, regardless of how much time elapses from infusion start to completion.

Sites will also record on source documents what the administration set was primed with (i.e., Sodium Chloride for Injection, 0.9%, study product from the study IV bag; see the fourth paragraph of the Infusions subsection in section 5.1) and that they have flushed the infusion set with Sodium Chloride for Injection, 0.9%, following the administration of the contents of the study IV bag.

For cohort 4, if an infusion rate is slowed for one administration, then all subsequent study treatment infusions will be performed at the slower infusion rate.

6.3.9 SC Injections

On the days indicated in the SOEs, study treatment will be administered by SC injection according to instructions provided in section 5.1 (timing and duration of injections) and section 5.3 (timing, syringe volume, number of syringes). Subcutaneous injections must be administered in the abdomen.

Record and key the following within 2 business days after the study treatment administration: dose administered, number of injections, the location of administration (i.e., which quadrant of the abdomen), whether the full dose was administered, the start and stop time of all SC injections, and will note the start and stop time of and reason for any interruption of the SC injections. Except in the case of SC injection site reactions, SC injections that are interrupted should be completed even if doing so exceeds the length of time in which the SC injections are expected to be completed (see section 5.3). The time of the completion of the set of SC injections will be known as Hour 0 for all participants, regardless of how much time elapses from start to completion.

6.3.10 Vital Signs and Targeted Symptom Assessment

Vital signs:
Vital signs (i.e., temperature, pulse, respiration rate, and blood pressure) will be assessed and recorded as indicated on the PK SOEs.

For Cohort 4, on the day of infusions #2 and #3, vital signs will be assessed and recorded at the time points indicated in the SOEs.

Targeted symptom assessment for infusions:
Beginning approximately 15 minutes after the infusion begins, information about the symptoms listed below should be actively solicited and recorded as indicated on the PK SOEs (Tables 6.1-2, 6.1-4, 6.1-8, and 6.1-10).

- Fatigue
- Feeling unwell
- Muscle aches
- Headache
- Chills
- Nausea
- Joint pain

For Cohort 4, on the day of infusions #2 and 3, information about the symptoms listed above should be actively solicited and recorded at the time points indicated in the SOEs.

Targeted symptom assessment for SC injections:
Within 15 minutes after the SC injection ends, information about the symptoms listed below should be actively solicited and recorded as indicated on the PK SOE for Arm C (Table 6.1-12).

- Fatigue
- Feeling unwell
- Muscle aches
- Headache
- Chills
- Nausea
- Joint pain
- Pruritus
- Pain/tenderness at injection site

In addition, within 15 minutes after the SC injection ends, information about the symptoms listed below should be obtained by direct observation and recorded.

- Bruising
- Erythema
- Swelling
- Change in body temperature
- Other local symptom/s

Resolution of Symptoms:
Clinicians will collect resolution information for any symptoms until the symptoms are resolved.

AE recording and reporting:
Refer to section 7.2 for AE recording and reporting requirements.

6.3.11 Pharmacokinetic (PK) Blood Collection

Refer to the LPC for collection, processing, storage, and shipping information.

For all Arm A and Arm B PK collections, blood must be drawn from the opposite arm from that used for the SAR441236 infusion. All non-PK blood collections and other evaluations listed for the infusion day must be completed before the PK collections begin.

PK blood collections, all of which are required, will be performed on the days and at the hours indicated in the SOEs, within the windows listed. Note that all post-infusion and SC injection collections are to be timed based on the end of the administration (Hour 0).

Beginning 1 week after the study treatment administration, a single blood collection will be performed at any time on the days indicated in the SOEs.

Section 11.0 includes details about the timing of collections.
Arm A, Cohorts 1-3
Participants may stay overnight to complete all of the collections required on the day of infusion and 24 hours after the infusion.

Arm A, Cohort 4
Participants may stay overnight to complete all of the collections required on the day of the 1st and 4th infusions and 24 hours after each of these infusions. Cohort 4 participants should not need to stay overnight on the day of the 2nd or 3rd infusion.

Arm B Cohorts
Participants may stay overnight to complete all of the collections required on the day of infusion and 24 hours after the infusion.

Arm C, Cohorts 10 and 11
Participants may stay overnight to complete all of the collections required on the day of SC injection and 24 hours after the SC injection.

6.3.12 ART Initiation or Re-initiation

Participants in Arm B are expected to initiate or re-initiate ART on Day **14** (Wk **2**).

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Recording and Reporting Requirements for This Protocol

If any of the AEs described below occur at any time during the study, they must be recorded and keyed within 2 business days.

- Grade ≥2 AE
- AE that led to a change in study treatment/intervention regardless of grade
- AEs meeting SAE definition or EAE reporting requirement
- Grade ≥1 rash
- Grade ≥1 urticaria

- Grade ≥1 angioedema
- Grade ≥1 ALT or AST evaluations or WBC count
- Grade ≥1 eosinophilia (see study-specific grading table below)
- All Grade ≥1 AIDS-defining illness

Grading Table for Eosinophilia, by Absolute Eosinophil Count

Grade	Value
1	≥1000/uL and <1499/uL
2	≥1500/uL and <1999/uL
3	≥2000/uL and <9999/uL
4	≥10,000/uL

Clinicians will collect resolution information for any symptoms until the symptoms are resolved.

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.http://rsc.tech-res.com/safetyandpharmacovigilance/

Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above).

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the **DAIDS** RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based

reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using 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 NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

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

7.3.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agents for which expedited reporting are required are: SAR441236 and placebo for SAR441236.

7.3.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is 2 weeks after each treatment administration. After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the **DAIDS** EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

The protocol Core Safety Team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation, data completeness, and adverse events.

The DAIDS clinical representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable.

The study will undergo interim reviews (as described in section 10.5) by an ACTG-appointed Study Monitoring Committee (SMC). The first interim review will occur no

more than 6 months after the enrollment of the first study participant. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statistician in consultation with the team. See section 10.5 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring will be outlined in a Study Monitoring Plan developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

Criteria for participant management, treatment interruption, and treatment discontinuation will be mandated only for AEs, toxicities, or laboratory abnormalities that are at least possibly related to SAR441236/placebo. Toxicities due to underlying HIV disease or drugs in the ART regimen should be managed according to standard clinical practice, with the goal of maintaining continuous ART. All participants who receive at least one administration of study treatment, including those participants who have an AE, regardless of attribution, are strongly encouraged to stay on study for the duration of the protocol to collect potential AE data and may continue study procedures unless clinically contraindicated.

8.1 Toxicity

Any AE or possible exacerbation of a pre-existing condition may be evaluated at the discretion of the study's core team as a treatment-related event.

The core team must be notified within 24 hours by email at actg.coreA5377@fstrf.org regarding any Grade 3 or 4 AE at any time.

The core team must be notified within 24 hours by email regarding any AE judged to be at least possibly related to SAR441236/placebo that results in the discontinuation of the study treatment administration. Unblinding may be requested (see section 10.7).

In Arm A Cohort 4, if any SAR441236/placebo infusion is discontinued, no future doses of SAR441236/placebo should be given to the participant.

For a toxicity that leads to a temporary interruption of an administration of SAR441236/placebo, the remainder of the dose and/or future doses may be given if the toxicity in question is determined not to be related to study treatment.

In the event that a Grade ≥2 proteinuria is detected, a nephrology consultation may be arranged along with any other clinically necessary investigations.

8.1.1 Grade 1 or 2 AE or Toxicity

Participants who develop a Grade 1 or 2 AE or toxicity during study treatment administration should be treated according to standard clinical practice and may

complete the study treatment administration at the discretion of the site investigator. Grade 1 or 2 AEs that are at least possibly related to SAR441236 must be documented.

8.1.2 Grade 3 AE or Toxicity

Participants who develop a Grade 3 AE or toxicity during study treatment administration that is judged to be at least possibly related to study treatment should have study treatment discontinued and the core team should be notified at actg.corea5377@fstrf.org.

Participants who develop Grade 3 AEs or toxicities following study treatment administration should be treated according to standard clinical practice and the core team should be notified at actg.corea5377@fstrf.org.

If an infusion is discontinued for a participant in the multi-dose Arm A Cohort 4, no future infusions of study treatment should be given, but the participant should remain on study (off-treatment, on-study), and the core team should be notified at actg.corea5377@fstrf.org.

Participants who develop a Grade 3 lab abnormality that is judged to be at least possibly related to study treatment will be followed closely until the abnormality resolves to Grade ≤2.

Participants who experience a Grade 3 AE that is judged not related to study treatment by the site investigator may continue study treatment at the discretion of the site investigator in consultation with the core team via actg.corea5377@fstrf.org.

8.1.3 Grade 4 AE or Toxicity

Participants who develop a Grade 4 AE or toxicity during study treatment administration that is judged to be at least possibly related to study treatment will have study treatment discontinued.

Participants experiencing Grade 4 AEs should be followed closely until resolution of the AE to Grade ≤2.

If an infusion is discontinued for a participant in the multi-dose Arm A Cohort 4, no future infusions of study treatment should be given, but the participant should remain on study (off-treatment, on-study).

Participants in any cohort who experience a Grade 4 AE that is judged not related to the study treatment by the investigator may continue study treatment and receive future infusions at the discretion of the site investigator in consultation with the core team via actg.corea5377@fstrf.org.

At any time post-study treatment administration, participants who experience a Grade 4 AE or clinical event that is thought to be related to the study treatment should remain on study (off-treatment, on-study) and the core team should be notified at actg.corea5377@fstrf.org.

If a Grade 4 lab abnormality occurs that is thought to be study treatment related, the participant will be followed until the abnormality resolves to Grade ≤2.

8.2 Other Conditions

Clinician and participant assessment of the local study treatment administration site will be conducted on the day of study agent administration and during the scheduled follow-up. Local parameters will include pain/tenderness, swelling, redness, bruising, and pruritis at the study treatment administration site/s.

Events that may require a clinic visit include rash, urticaria, fever of 38.6°C (Grade 2) or higher lasting more than 24 hours, or significant impairment in the activities of daily living. Additionally, arthralgia or other clinical concerns may prompt an additional study visit based on the judgment of a study clinician. Serum sickness, characterized by a pruritic rash with fever of greater than 38.6°C or higher, and myalgia/arthralgia out of proportion to any joint swelling, is of particular concern. Clinical laboratory assays and clinical evaluations will assess safety and tolerability at specified intervals after each administration.

Urticaria may develop during study treatment infusion or within 24 hours to 2 weeks thereafter, most commonly without local or systemic reactogenicity or a change in vital signs. Urticaria and any systemic symptoms that occur should be managed by local standard of care, which may include administration of antihistamines and/or oral or IV corticosteroids for more severe reactions. Possible discontinuation of study treatment infusion must be discussed with the study's core team via email at actg.corea5377@fstrf.org.

8.3 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancy outcomes will be summarized in the final study report.

Pregnancy Outcomes and Reporting

If a **participant** has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact **the participant** regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

Pregnant **participants** must discontinue study treatment, but will remain on study for at least 12 weeks after stopping treatment, completing safety evaluations as indicated in the LPC. Some blood for stored samples may be collected during this time, if feasible.

Pregnant **participants** who remain on study through study end will complete the study discontinuation visit when they discontinue study participation. The off-study eCRF must be completed at the end of the pregnancy. The outcome and AEs for the participant and infant will be recorded on an outcome eCRF.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Study treatment-related toxicity (see section 8.1).
- SAE related to study treatment (see section 7.2).
- Requirement for prohibited concomitant medications (see section 5.5.2).
- Pregnancy or breastfeeding.
- Request by participant to terminate treatment.
- Clinical reasons believed life-threatening by the physician, even if not addressed in the toxicity section of the protocol.

9.2 Premature Study Discontinuation

- Failure by the participant to attend three consecutive clinic visits.
  - NOTE: This criterion is not applicable if visits **can be** conducted remotely, as described in section 6.2.3.
- Pregnancy or breastfeeding (see section 8.3 for follow-up requirements).
- Request by the participant to withdraw.
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant.
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol so as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the ACTG, IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5377 is a prospective, double-blinded, and randomized (within dose group for Arms A and C), placebo-controlled (for Arms A and C), phase I, first-in-human study designed to evaluate the safety, pharmacokinetic, virologic and immunologic effects of single-dose and multiple-dose SAR441236 in both suppressed participants on ART (Arms A and C) and viremic participants (Arm B) with HIV. Each arm has multiple cohorts (Cohorts 1-4 in Arm A, Cohorts 5-**8** in Arm B, and Cohorts 10 and 11 in Arm C), evaluating SAR441236 at doses of 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 30 mg/kg. Participants in Cohorts **1, 2, 3, 5, 8, 10, and 11 (and, if it is opened, Cohort 7)** will receive a single dose of SAR441236 (or placebo for Cohorts 1-3 and 10-11) and be followed for 24

weeks, while the participants in Cohort 4 will receive 4 doses of 30 mg/kg SAR441236 or placebo and be followed for **36** weeks **after their final infusion**. One third of participants in each cohort in Arms A and C will receive placebo, and all participants in Arm B will receive SAR441236 only.

Across all sites, study treatment at a given dose in Arm A **was** not administered to the third participant until at least the day after the last of the first two participants **had** received study treatment. Across all sites, no more than two receive**d** study treatment at a given dose in Arm C within a single week. The first two enrollees at a given dose in any arm may receive study treatment on the same day. For Arms A and C, no more than two participants may begin study treatment at a given dose on the same day. Cohort 1 (Arm A) and Cohort 5 (Arm B) opened to accrual simultaneously. For Arms A and C, the decision to open to accrual for each successively higher dose cohort **was** based on Core Safety Team (CST) review of the safety data from the first 14 days of the previous dose cohort unless an SMC review is triggered (see details in section 10.5). For Cohort 4, enrollment **was** paused after the first six participants are enrolled. The Day 14 safety data for these six participants **was** reviewed by the CST before the decision to resume enrollment and continue subsequent infusions **was** made.

Under Version 3.0, the latest Arm B cohort that was opened under Version 2.0 **(Cohort 5, 1 mg/kg) was** closed to enrollment. Arm B Cohort 8 (30 mg/kg) **was** then opened because the 30 mg/kg dose was identified as the highest tolerated dose in Arm A based on a CST review of Day 14 safety data for the first six enrolled participants in Arm A Cohort 4 (30 mg/kg). **Under Version 4.0 of the protocol, Cohort 6 was removed from Arm B.** The decision to open **Cohort 7** will be based on CST reviews of the efficacy data from the first 14 days of **Cohort 8** (see details in section 10.4.2). Because 14-day safety data from all Arm A cohorts were available prior to the implementation of Version 3.0, CST review of safety data from the first 14 days of each Arm B cohort will be performed but these results will not be used to determine whether to open the next cohort.

Analyses and dissemination of study results might commence by groups of cohorts as appropriate. **Study** interim results **may** be shared with **the industry supporter** for the purpose of drug development.

10.2 Outcome Measures

10.2.1 Primary Outcome Measures

10.2.1.1 Safety and tolerability

Occurrence of a Grade ≥3 AE that is related to study treatment (as judged by the CST, blinded to active/placebo treatment in Arms A and C) any time from study treatment administration through the entire follow-up (**36** weeks **after the final infusion** for Cohort 4 and 24 weeks for other cohorts).

10.2.1.2 Pharmacokinetics

AUC_{12wk} of SAR441236 (see section 11.0).

10.2.1.3 Efficacy

Change in plasma HIV-1 RNA (log_{10} copies/mL) from baseline (defined as the last measurement taken prior to the treatment initiation) to Day 7 of monotherapy for viremic participants with HIV (Arm B cohorts).

10.2.2 Secondary Outcome Measures

10.2.2.1 Plasma HIV-1 RNA (copies/mL) at baseline and post infusion for viremic participants with HIV (Arm B cohorts).

10.2.2.2 Change in plasma HIV-1 RNA (log_{10} copies/mL) from baseline (defined as the last measurement taken prior to treatment initiation) to Day **7** and Day **14** of monotherapy, and maximum reduction during **14** days of monotherapy for viremic participants with HIV (Arm B cohorts).

10.2.2.3 Attributions of anti-SAR441236 antibodies in all cohorts.

10.2.2.4 Change in $CD4^+$ T cell counts (cells/mm^3) from baseline to week 12 following single dose of SAR441236 for all cohorts and the change in $CD4^+$ T cell counts (cells/mm^3) from baseline to week 12 following each infusion for Cohort 4.

10.2.2.5 Pharmacokinetic parameters (see section 11.0) of SAR441236 following each infusion or SC injection.

10.2.2.6 Establish concentration (or dose)-response relationship between SAR441236 exposure and changes in plasma HIV-1 RNA from entry baseline to week **2** (or viral load nadir) for Arm B cohorts.

10.2.3 Other Outcome Measures

10.2.3.1 Change in neutralization titers

10.2.3.2 HIV-1 *env* sequence phylogenies

10.2.3.3 High-throughput quantitative full-length HIV-1 *env* sequencing

10.2.3.4 Baseline phenotypic susceptibility of plasma HIV-1 species

10.2.3.5 Phenotypic susceptibility testing of archived HIV-1 *env* species

10.2.3.6 HIV-specific $CD8^+$ T cell activity

10.2.3.7 Total HIV-1 DNA and caRNA levels

10.2.3.8 Change in plasma HIV-1 RNA measured by SCA

10.2.3.9 Relationships between hsCRP levels and PK parameters

10.3 Randomization and Stratification

Cohorts within each arm will enroll sequentially. Within each cohort in Arm A and Arm C, participants will be randomized 2:1 in a double-blind fashion to receive SAR441236 (n=8 in Cohort 4 and n=4 for other cohorts) or placebo (n=4 in Cohort 4 and n=2 for other cohorts). Randomization will use the permuted block method without institutional balancing or stratification. After the enrollment of each dose cohort is complete, study enrollment for that arm will be suspended until a decision is made on opening the next cohort to enrollment, based on the criteria for dose escalation (Arm A and Arm C) or de-escalation (Arm B) and, when triggered, the SMC review (see section 10.5).

10.4 Sample Size and Accrual

The total sample size of this study is **53-65** evaluable participants (**39-51** active-treated participants and 14 placebo participants). An evaluable participant is one who has received at least 90% of their first or only dose of study treatment **and for Arm B, beginning with Version 4.0 of the protocol, has an entry plasma HIV-1 RNA ≥5000 copies/mL**. Cohort 1 (Arm A) and Cohort 5 (Arm B) opened to accrual simultaneously. The enrollment of the first six Cohort 4 participants **was expected to** take place within 8 weeks to ensure enough safety data are available in a timely manner for the decision to continue with subsequent doses; accrual of the rest of Cohort 4 participants **was** held until Day 14 safety data for the first six enrolled participants **were** reviewed by the CST.

In all cohorts, participants who do not receive study treatment, or who receive less than 90% of their first or only intended infusion or SC injection dose will be replaced. Arm A or Arm C participants who discontinue the study prior to Day 14 without having met the primary safety endpoint (section 10.2.1.1) **were** replaced to ensure enough safety data **were** available for dose escalation evaluation. Arm B participants who discontinue the study prior to Day 14 without sufficient virology data (as judged by the CST)**, or beginning with Version 4.0 of the protocol, who have an entry plasma HIV-1 RNA <50 copies/mL,** will be replaced to ensure enough efficacy data are available for dose de-escalation evaluation. The CST may decide on additional replacements if primary endpoints cannot be adequately assessed due to missing data or incorrect infusion procedure. Participants who initiate the infusion or SC injection but receive less than 90% of their first or only intended dose will be encouraged to remain on study and complete all study follow-up.

10.4.1 Safety

Arm A and Arm C dose escalation criteria (for Cohorts 1-3 and 10) and multiple infusions continuation criteria (for Cohort 4) for consideration by the SMC are defined as:

a) No more than two participants experience a Grade 3 AE that is probably or possibly related to study treatment (as judged by the CST, blinded to active/placebo treatment) prior to or on Day 14 after treatment administration; and
b) No more than one participant experiences a Grade 3 AE that is probably related to study treatment (as judged by the CST, blinded to active/placebo treatment) prior to or on Day 14 after treatment administration; and
c) None of the participants experiences a Grade ≥3 AE that is definitely related to study treatment or that is Grade ≥4 and probably or possibly related to study treatment (as judged by the CST, blinded to active/placebo treatment) prior to or on Day 14 after treatment administration

Table 10.4-1 below shows the probabilities of dose escalation under various assumed true rates for two types of AEs as described above. In the table, the column “True rate of Grade 3 AE possibly related to study Rx” is the probability conditional on not having the “Grade 3 AE probably or definitely related or Grade 4 or higher AE probably or possibly related to study Rx.” The column “True rate of Grade 3 AE probably related to study Rx” is the probability conditional on not having the “Grade 3 AE definitely related or Grade 4 or higher AE probably or possibly related to study Rx”. The column “True rate of Grade 3 or higher AE definitely related or Grade 4 or higher AE probably or possibly related to study Rx” is the unconditional probability of the event.

There **were** four participants in each of Cohorts 1-3 and 10 receiving active treatment. The sample size provides a reasonably high probability of dose escalation when the true event rates are, in fact, acceptable. For example, if the true rate of a participant in the active treatment arm of a given dose cohort experiencing a Grade 3 AE that is possibly related to study treatment is 0.015 (i.e., 1.5%), and the true rate of a Grade 3 AE that is probably related to study treatment is 0.012 (i.e., 1.2%), and the true rate of Grade 3 AE that is definitely related or Grade 4 or higher AE that is probably or possibly related to study treatment is 0.010 (i.e., 1%), then the probability that the study will dose escalate to the next higher dose is 0.96 (i.e., 96%) for Arm A or Arm C. Given that this is an acceptable safety profile, this means that the probability of incorrectly concluding the current dose unsafe is 0.04 for Arm A or Arm C. On the other hand, the proposed sample size provides a low probability of dose escalation when the true event rates are unacceptable. For example, if the true rate of Grade 3 that is possibly related to study treatment is 0.260 (i.e., 26%), the true rate of Grade 3 AE that is probably or possibly related to study treatment is 0.240 (i.e., 24%), and the true rate of Grade 3 AE that is definitely related or Grade 4 or higher AE that is probably or possibly related to study treatment is 0.20 (i.e., 20%), then the probability of dose escalation is only 0.27 (i.e., 27%) for Arm A or

Arm C, and the corresponding probability of not dose escalating and correctly concluding the dose unsafe is high at 0.73 for Arm A or Arm C.

Table 10.4-1: Probabilities of Dose Escalation under Various Assumed True Rates for Participants Receiving Active Treatment in Cohorts 1-3 and 10 (N=4/cohort)

True Rate of Grade 3 AE Possibly Related to Study Rx	True Rate of Grade 3 AE Probably Related to Study Rx	True Rate of Grade 3 or Higher AE Definitely Related or Grade 4 or Higher AE Probably or Possibly Related to Study Rx	Probability of Dose Escalation
0.007	0.006	0.005	0.98
0.015	0.012	0.010	0.96
0.03	0.024	0.020	0.92
0.04	0.036	0.030	0.88
0.052	0.048	0.040	0.84
0.08	0.060	0.050	0.79
0.15	0.120	0.100	0.59
0.2	0.180	0.150	0.42
0.26	0.240	0.200	0.27
0.4	0.360	0.300	0.09

10.4.2 Efficacy

Existing small clinical trials using bNAbs (with dosing ranging from 1 mg/kg to 40 mg/kg) without ART for viremic participants [Caskey 2015, Caskey 2017, Lynch 2015] showed the maximum reduction in plasma HIV-1 RNA is achieved around Day 7 following a single dose infusion, with the reduction ranging from -0.1 to 2.5 $\log_{10}$ copies/mL and with a mean around 1.0 $\log_{10}$ copies/mL. For the purposes of dose de-escalation in the Arm B cohorts, a virologic response to the study treatment will be defined as having an HIV-1 RNA reduction of at least 1.0 $\log_{10}$ copies/mL from baseline. With that definition, the dose de-escalation criteria for an Arm B cohort are:

a) At least three participants with a virologic response by Day 14

OR

b) If only 2 participants have a virologic response by Day 14, 6 additional participants will be enrolled in the same dose cohort, and at least 6 of the 12 participants show a virologic response by Day 14.

Table 10.4-2 below shows the probability of dose de-escalation under various response rates. The proposed criteria provide a reasonably high probability of dose de-escalation when the true response rate is acceptable. For example, if the true response rate for a given dose cohort is 70%, the probability of dose de-escalation is 0.97 (i.e., 97%). On the other hand, the proposed criteria provide a low probability of dose de-escalation when the true response rate is

unacceptable. For example, if the true response rate for a given dose cohort is 30%, the probability of dose de-escalation is only 0.28 (i.e., 28%). Note that when fewer than 2 participants have a virologic response, even if an additional 6 participants are enrolled, the probability that 6 of 12 participants will have a virologic response is ≤0.01, assuming the true response rate is ≥50%. For that reason, the CST will consider stopping Arm B without enrolling additional participants or opening lower dose cohorts when fewer than two of six participants have a virologic response by Day 14.

Table 10.4-2: Probabilities of Dose De-escalation under Various Assumed True Response Rates for Participants in **Arm B** Cohorts

True Response Rate	Probability of Dose De-escalation
70%	0.97
60%	0.89
50%	0.74
40%	0.51
30%	0.28

The study has 80% power to detect a drop of 1.7 $\log_{10}$ copies/mL in plasma HIV-1 RNA in each cohort with N=6.

10.5 Data and Safety Monitoring

Accrual, baseline characteristics, conduct of the study, all toxicities, HIV-1 RNA, and AEs will be monitored during the trial with reports broken down by dose cohort sent to the CST on a regular basis. The CST will review the individual safety data frequently to assess the relationship of all reported toxicities and AEs to the study treatment in blinded assessments (from Arm A and Arm C), incorporating the site investigator's opinion in their relation to the treatment reported on the eCRFs.

The study will undergo SMC review approximately every 6 months, with the first review scheduled no more than 6 months after the enrollment of the first participant. In addition, after the data are available from Day 14 follow-up for the last enrolled participant in each of Cohorts 1-3 and 10, and the sixth enrolled participant in Cohort 4, if there is any Grade 3 or higher AE that is at least possibly related to study treatment, all safety data, including the decision on the relationships between AEs and study treatment, will be reviewed to determine whether to dose escalate (for Cohorts 1-3 and 10) or continue with multiple infusions (Cohort 4); otherwise, a summary letter on safety data will be sent by the study chair to the SMC and dose escalation (Cohorts 1-3 and 10) or multiple infusions (Cohort 4) will proceed without a pause. Although the suggested dose escalation (or continuation of multiple infusion) criteria are based on Day 14 safety outcomes for all participants in the previous cohort (or the first six participants in Cohort

4), all available safety information from both arms at the same dose level will be provided in the SMC report and the summary letter to the SMC for a complete review.

If at any time within a given dose cohort in any arm
a) three or more participants experience a Grade 3 AE that is probably or possibly related to study treatment (as judged by the CST, blinded to active/placebo treatment), or
b) two or more participants experience a Grade 3 AE that is probably related to study treatment (as judged by the CST, blinded to active/placebo treatment), or
c) one or more participant experiences a Grade ≥3 AE that is definitely related to study treatment or that is Grade ≥4 and probably or possibly related to study treatment (as judged by the CST, blinded to active/placebo treatment), or
d) one or more participants experiences an SAE that is possibly, probably, or definitely related to study treatment (as judged by the CST, blinded to active/placebo treatment),

enrollment into the study will be temporarily suspended, subsequent infusions (Cohort 4 only) will be put on hold, and the SMC, unblinded to active/placebo treatment, will be asked to review all safety data; review the relation to study treatment of the event(s) thought by the blinded CST to be a primary safety outcome; and recommend how the study should proceed with respect to resuming enrollment, continuing study treatment, and dose escalation.

For Arm B, after the data are available from Day 14 follow-up for the last enrolled participant in Cohort 8, efficacy data will be reviewed by the CST (see section 10.4.2) to determine whether to dose de-escalate.

10.6 Analyses

10.6.1 Primary Analyses

For the primary safety analysis, AEs attributed to study treatment (section 10.2.1.1) will be described separately for the active treatment group of each dose cohort, and for the combined placebo groups (Arms A and C only). All participants who have been exposed to the study treatment/placebo will be included in this analysis. As secondary analyses, all other reported AEs will be summarized for the treatment arm of each dose cohort, and combined placebo arm.

For the primary PK outcome (section 10.2.1.2), descriptive summaries of estimated AUC (section 11.0), by dose group, will be presented. Difference between same dose cohorts (viremic vs. virologically suppressed) will be evaluated using linear model with natural log transformed AUC values. The between-cohort comparison will be “as-treated” such that only participants actually receiving ≥90% of intended dose will be included.

For the primary efficacy analyses for Cohorts 5-9 (section 10.2.1.3), reduction in plasma HIV-1 RNA (log_{10} copies/mL) from baseline to Day 7 following a single

infusion will be summarized, both in combined cohorts and in each cohort separately. Efficacy analyses will be "**per protocol**" such that only participants actually receiving ≥0.9 mg/kg SAR441236**, and with an entry plasma HIV-1 RNA ≥5000 copies/mL** will be included. Comparison between pre- and post-treatment will be made using Wilcoxon signed rank test for each cohort.

10.6.2 Secondary Analyses

Longitudinal participant-specific plots for antiviral activity during the 28 days post infusion will be presented for each participant in Arm B. A mixed-effect model will be used to estimate individual viral decay rates. Plasma HIV-1 RNA will be compared pre-treatment to Days 14 and 28 post-treatment using paired t-tests. Descriptive statistics will be provided for the maximum reduction for each participant during 28 days of monotherapy. Because low-level viremia as measured by SCA is anticipated to be below assay limit in a substantial fraction (~50%) of Arm A and Arm C participants, binary or categorical analysis approaches are planned to assess treatment effects on SCA.

Descriptive summaries, by dose group, will be presented for the estimated PK parameters (see section 11.0). Graphical approaches will display concentration curves over time. Graphical displays and correlation analyses will investigate dose-response relationships with respect to change in plasma HIV-1 RNA from baseline to week 4 across the dose groups in relation to PK parameters estimated as outlined in section 11.0.

The timing of treatment effects on immunologic and virologic outcome measures will be investigated by identifying, for each measure, the post-treatment time point with the greatest magnitude change from baseline. It is also of interest to evaluate whether there is evidence that the second infusion of treatment further "boosts" responses following the first dose in Cohort 4.

10.7 Unblinding

In the rare instance that a determination is made to unblind a participant's treatment, sites should follow the instructions provided in the Emergency Unblinding Individual Participants section of the current version of the ACTG Unblinding Participants Standard Operating Procedure (SOP).

Any decision to unblind Arm A or Arm C as a whole will be made by the CST in conjunction with the ARTS TSG and the Scientific Agenda Steering Committee (SASC), based on a recommendation from the SMC or the results of another trial (see also the DAIDS SOP "Termination of a Trial or a Single Treatment Arm"). In such a case, participants will be unblinded as soon as possible (if in Arm A or Arm C), beginning with the DMC's sending treatment assignments to the sites when directed by the team to do so. Sites will be directed to make every effort to contact all participants, including those who have completed follow-up, to explain the study results to them.

If Arm A or Arm C is unblinded based on an interim analysis, the results of the interim analysis will be published. Data from visits that occurred before the interim analysis but that were not in the database at the data cutoff date have little potential for bias and may be reported with a comment. Data from visits that occurred after unblinding are potentially biased and must not be used if the intent is to claim that all the data are from a blinded study. In unblinding of Arm A or Arm C is undertaken due to both an interim analysis and results from other trials, the conditions under which potentially biased study data were gathered must be made clear in any publication.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

This is a first-time-in-human, phase I, single ascending dose and fixed multiple-dose study. As such, the pharmacology objectives are:

11.1.1 To understand the pharmacokinetics of SAR441236 in humans at 1, 3, 10, and 30 mg/kg as single dose infusions, at 30 mg/kg following multiple infusions, and at 0.3 and 1 mg/kg single SC injections. All pharmacokinetic parameters will be estimated using non-compartmental analyses.

11.1.2 To apply a population pharmacokinetic model to the concentration-time data. A pre-clinical model has already been developed and these data will be added to the overall dataset.

11.1.3 To establish concentration (or dose)-response relationships between derived pharmacokinetic parameters (or dose) and changes in plasma HIV-1 RNA from baseline to week 4. Variables other than viral load may also be examined.

11.2 Pharmacology Study Design

Note that infusions in Cohorts 1, 2, **and** 5 are expected to be completed in approximately 30 to 60 minutes, while those in Cohorts 3, 4, and 8**, and, if it is opened, 7** are expected to be completed in approximately 60 to 90 minutes. Post-dose PK collections will take place relative to the time that the study treatment administration (either infusion or the set of SC injections) ends.

Blood for PK will be collected as shown in the Administration/PK/HIV-1 RNA Timing SOEs (Tables 6.1-2, 6.1-4, 6.1-5, 6.1-6, 6.1-8, 6.1-10, and 6.1-12).

11.3 Primary and Secondary Data, Modeling, and Data Analysis

Pharmacokinetic parameters from all PK evaluations will be completed using Phoenix WinNonlin. Parameters will include AUC_{inf} and AUC_t from single doses and AUC_{12wk} for multiple doses. Other parameters such as half-life ($t_{1/2}$), clearance (CL), distribution volume (V), absolute bioavailability (F), maximum concentration (C_{max}), time to C_{max} (T_{max}), and trough will also be calculated and trough concentrations will be reported.

These parameters will also be determined following SC administration in Arm C (Cohorts 10 and 11) in order to calculate SC PK parameters and determine the absolute bioavailability of SAR441236 relative to the same IV dose(s) in Arm A and/or Arm B.

11.4 Anticipated Outcomes

Results from this study will generate a new understanding of SAR441236 pharmacokinetics in humans, identify target therapeutic concentrations for SAR441236, and determine the bioavailability of SC administration.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration/randomization.

12.2 Role of Data Management

12.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity [FDA 2021]. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solutions. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol**, including** the informed consent document and any subsequent modifications**,** will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other local, US, or non-US authorities as part of their duties, or the industry supporter or designee.

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, other government agencies as part of their duties to ensure that research participants are protected, or by the industry supporter.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion 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 National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I: A5377 **ARM B** STUDY VISIT SCHEDULES AND DESCRIPTION OF VISITS AND EVALUATIONS

Section 1: **Arm B** Study Visit Schedule
*Upon IRB approval **of the protocol document**, sites may **decide whether to provide** the table **below or the information that follows** to study candidates **or participants or to incorporate any/all of it** into site-specific consent form.*

Arm B, Dosing Groups **8 and 7**

Evaluation – what will happen during the visit	Screening visit	Entry visit - Day 0[1]	D. 1	D. 2	D. 3	D. 4	D.7 (week 1)	D. 10	Wk. 2	Wk. 3	Wk. 4	Wk. 8	Wk. 12	Wk. 24	If you leave the study early
Visit windows→							*±1 day*		*±2 days*			*±7 days*			
Consent	√														
Physical examination	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Questions about your health and medications you are taking	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Blood collected		√	√	√	√	√	√	√	√	√	√	√	√	√	√
Fasting blood collection	√														
Hepatitis screen		√													
Urine test		√							√				√		√
Pregnancy test	√	√	If necessary												√
Infusion of study treatment		√													
Blood collected six times over 10 hours		√													
Start **or re-start** ART									By wk **2**						

[1] You may stay overnight the day that you receive the infusion.

Section 2: Description of Visits and Evaluations

Screening Visit

If you decide that you want to be in this study, you will have some tests to see if you are able to enter the study. *(The screening visit will take about XX hours.)*
At the screening visit:

- You will be asked about your health and medicines you have taken in the past or are taking now.
- You will have a complete physical exam including signs and symptoms, diagnoses, vital signs (temperature, pulse, respiration rate, and blood pressure), and height. Your weight will be measured at this visit.
- You will have blood drawn for the following purposes:
  - routine lab tests for safety
  - to measure the amount of HIV in your blood cells
  - to measure your CD4+ and CD8+ cell counts (cells that help fight infection).
- If you are a woman able to become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant. You will not be able to enroll in this study if you are pregnant.

Entry (Day 0)

If you are eligible for the study, you will come in for a study Entry visit. **You should fast before this visit (nothing to eat or drink for at least 8 hours before you arrive).** This visit will take about 12 hours and will probably require an overnight stay in a special research facility. At this visit:

- You will have a brief physical exam, including vital signs **and weight measurement**.
- You will be asked about your health and any changes in your medicines since your last visit.
- You will have a urine lab test
- You will have *(about X tablespoons [XX mL] of)* blood drawn for the following purposes:
  - virologic studies (to measure the level of HIV in the blood and to isolate the HIV virus)
  - routine lab tests for safety
  - **hepatitis screen (a test for liver disease)**
  - to measure the amount of HIV in your blood
  - to measure your CD4+ and CD8+ cell counts; and to measure the amount of anti-SAR441236 antibodies in your blood.

Some of the blood you provide will be stored for future protocol-required virologic and immunologic testing.

If you are able to become pregnant, you will be asked to give a urine or a blood sample to see if you are pregnant. You will not be able to enroll in this study if you are pregnant.

On the day that you receive the study treatment, you will need to stay in the clinic *(or General Clinical Research Center)* during the infusion. You will need to be available for at least 10 hours after the infusion and then again about 24 hours (1 day) after the infusion, so you might be asked to stay overnight.

Your vital signs will be checked and you will be checked for any side effects from the study treatment at the following times:

- **i**mmediately before the infusion
- during the infusion

- immediately after the infusion
- multiple times over the 10 hours after the infusion.

Vital sign checks and checks for side effects will be repeated at each study visit for the next 2 weeks.

You will have blood collected at the following times:
- immediately before the infusion
- immediately after the infusion
- multiple times over 10 hours after the infusion
- once more 24 hours (1 day) after the infusion

The blood that is collected during this time *(which will be about xx mL total)* will be used to look at the levels of study treatment in your blood over time. This is called “PK testing”.

The infusion is expected to take 60 to 90 minutes. The infusion might take longer if there is a problem with the machine or if the doctor thinks that it is in your best interest to give you the study treatment over a longer period of time (including stopping and re-starting it).

Study Visits
You will return to the clinic for study visits as shown in the table above. **Most** study visits will last about 1 hour. **T**he final follow-up visit will be at Week 24, or about 6 months after you enter the study.

If you are unable to come to the clinic because of illness or the site is unable to conduct non-essential study visits, then some of your scheduled study visits may be conducted remotely (for example, by telephone or telehealth). It is possible that your time on the study may be extended if your final visit is scheduled to take place when you are not able to be seen in the clinic. In this situation, your final visit will take place only when it is possible to conduct a face-to-face visit with you.

What will happen during most study visits
- You will be asked about your health and any changes in your medicines since your last visit.
- You will have a brief physical exam including vital signs and a weight measurement.
- 2 **and 12** weeks after your study treatment **infusion**, you will have a urine test
- You will have blood *(about XX to XX tablespoons [XX to XX mL])* drawn for some or all the purposes listed below:
  - to measure the amount of SAR441236 in your blood
  - to test for the presence of antibodies to SAR441236 (produced by your immune system)
  - PK studies
  - virologic studies
  - storage for future protocol-required virologic and immunologic testing
  - CD4+ and CD8+ cell counts
  - HIV viral load testing
  - safety blood tests.
- If you think that you might be pregnant at any time then you will have a pregnancy test.

(The total amount of blood that will be drawn for participants in Arm B is XXX tablespoons [XX mL].)

INFORMED CONSENT FORM
AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

Sponsor / Study Title:	**National Institute of Allergy and Infectious Diseases / "A Phase I, First-in-Human Study of SAR441236, a Tri-specific Broadly Neutralizing Antibody, in Participants with HIV"**
Protocol Number:	**A5377**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

SUMMARY

PURPOSE: The purpose of this study is to test the safety of SAR441236, a study drug that has not been tested in humans before now. **This is the first study of SAR441236 in people.**

The study will also look at how long SAR441236 stays in the body after one dose and after four doses. It will also look at whether SAR441236 can reduce the level of HIV (the virus that causes AIDS).

NUMBER OF PARTICIPANTS:
Between 53 and 65 participants **are expected to** be enrolled into **up to 9** different dosing groups.

LENGTH OF STUDY:
The study will last about 6 months for most people. For one group of study participants (known as Dosing Group 4), the study **lasted longer** because the study drug **was** given 4 times at about 3-month intervals **(which took at least 9 months)**.

NOTE: Enrollment to and follow-up of Dosing Group 4 has been completed. All participants enrolling to Version 4.0 of the study will be on study for about 6 months.

You may need to stay at the clinic all day and then overnight on the day that the study starts. You will then need to come back to the clinic **up to 8** more times in the first 4 weeks. For most people, over the last 5 months of the study, there will be 3 clinic visits.

STUDY TREATMENT:
SAR441236 is a broadly-neutralizing antibody (or "bNAb"). The results from tests in animals and in the lab suggest that SAR441236 may have activity against HIV.

In this study, there are three study treatment categories, which we are calling "arms" (Arm A, Arm B, and Arm C). Depending on which arm you are in, you will be given study treatment through a vein in your arm or by an injection just under the skin on your abdomen (stomach). In two of the arms (Arm A and Arm C), study treatment could be SAR441236 or a placebo (an inactive substance). In one arm (Arm B), everyone will be given SAR441236.

NOTE: All participants enrolling into Version 4.0 of the study will be in Arm B and so will receive SAR441236 one time through a vein in the arm.

Up to five different doses of SAR441236 will be tested in this study. You will receive only one dose that will be based on when you enter the study. Anti-HIV medications (also known as "ART") will not be provided through the study but you will be required to be on ART for most or all of the time that you are in the study.

If you are in Arm A or Arm C, you will remain on your current ART throughout the study.

If you are in Arm B, **you will receive SAR441236 about 2 weeks before you start or re-start ART. Note that this study treatment plan is different from the current standard treatment for HIV, which recommends that HIV treatment begin as soon as possible after an HIV diagnosis or when the level of HIV in your blood is high. The study treatment plan has been approved by the US Food and Drug Administration (FDA). Y**ou must be willing to start or re-start ART by the **14th** day **(week 2)** of the study. The ART must be expected to be effective for you.

ACTIVITIES:

Blood and urine collections
At most visits, some blood will be collected from a vein in your arm. At a few visits, you will be asked to provide a urine sample.

Special procedures
If you are in the infusion Dosing Groups (in Arm A or Arm B), study treatment will be given to you through a vein in your arm. This will take about 30 to 60 minutes or about 60 to 90 minutes depending on which dose of study treatment you are taking. You will need to remain still in a semi-reclining position while you receive SAR441236.

If you are in one of the subcutaneous injection groups (in Arm C), study treatment will be given to you as one, two, or three injections just under the skin on your abdomen. It will take 5 to 15 minutes to administer these injections. ("Subcutaneous" means "under the skin.")

Several samples of blood will be collected from you on the day that you receive study treatment. You will need to stay in the clinic or be able to return at specific times for up to 24 hours after receiving SAR441236.

RISKS: Because SAR441236 **had** not been tested in humans before **this study**, **all** specific risks are not known. We do know, however, that the following are possible when an antibody, the type of drug that SAR441236 is, is given to people:

- Anaphylaxis – an allergic reaction that may occur soon after an antibody product is given. It includes:
  - Difficulty breathing
  - Low blood pressure
  - Hives or rash
  - Swelling in the mouth and on the face
- Serum sickness - a delayed allergic reaction that may occur several days to 3 weeks after an antibody product is given. It includes:
  - Hives or rash
  - Fever
  - Enlarged lymph nodes
  - Muscle pain
  - Joint pain or swelling
  - Chest discomfort
  - Shortness of breath
- You may also experience an increase in liver enzymes, a blood test that can be a sign of liver damage.

BENEFITS: No direct benefits should be expected from participating in this study.

OTHER CHOICES:

Instead of being in this study, you have the option of continuing with your current ART or starting **or re-starting** ART under the care of your regular doctor or other health care provider.

INTRODUCTION

The purpose of this study is to test a study drug that **had** not been tested in humans before now. This experimental drug is called SAR441236.

You are being asked to consider taking part in this research study because you are living with HIV and you either

- Have been taking ART for at least 12 months and HIV cannot be found in your blood using standard clinical tests
  or
- You have never taken ART or have not taken ART in the past **8 weeks** and HIV can be found in your blood using standard clinical tests. You must be **able and willing** to start or re-start ART **approximately 2 weeks after you enter the study and receive a single dose of SAR441236. Note that this is not the standard current treatment for HIV. (See the Arm B paragraph in the STUDY TREATMENT section, above.)**

This is a research study that is designed to answer scientific questions about a new drug. Only people who want to participate in research will be part of this study. You can discuss the study with others

before deciding to join. No matter what your decision is, any other care that you get at this clinic will not change.

This study is sponsored by the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and the AIDS Clinical Trials Group (ACTG). The doctor in charge of this study at this site is listed on the first page of this form and is referred to throughout this form as the "study doctor." Before you decide if you want to be a part of this study, we want you to know more about it.

This consent form gives you information about this study. The study staff will talk with you about this information and will answer any questions that you have about this study at any time. You may decide not to take part in the study.

If you do decide to take part in this study, you will be asked to sign and date this consent form and you will get a copy to keep. After you join the study, you may decide to stop taking part in the study at any time.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to investigate:

- If one infusion or one set of subcutaneous injections of SAR441236 is safe and tolerable
- If one infusion of SAR441236 can reduce the amount of HIV in a person's blood (in people not taking ART)
- If multiple infusions (up to four) of SAR441236 are safe and tolerable
- If receiving multiple infusions of SAR441236 can reduce the amount of HIV in a person's blood more than receiving just one infusion

And to collect information about the amount of SAR441236 in your blood over time (also known as "PK testing").

This study will help determine how long SAR441236 lasts in the body after a single dose. In addition, we will get some preliminary information about whether SAR441236 has any effect on the viral reservoir (the amount of HIV that cannot be found by standard clinical tests) in people already on a suppressive ART regimen. This information will help determine what dose of SAR441236 to use in future studies of this antibody for possible treatment, prevention, and HIV elimination.

SAR441236 is a broadly-neutralizing antibody (or "bNAb") that has been tested in the lab and in animals. The results of these tests suggest that SAR441236 may have activity against HIV. The next step is to test whether SAR441236 is safe and has anti-HIV activity in people. The US Food and Drug Administration (FDA) has approved this study, A5377, of SAR441236 in people. Information from this and other studies of SAR441236 could be used by the FDA and other regulatory entities to evaluate whether more studies should be done with SAR441236. Information from this study may be used to obtain FDA approval of SAR441236 in the future.

An antibody is a type of protein that helps the body fight infections. Antibodies are usually made by a person's own immune system, but they can also be manufactured like a drug, which is how SAR441236 is made, and then given either for the treatment or for the prevention of a disease.

Antibodies that develop naturally against HIV attach to one part of the virus so that the body's immune system can try to attack it. SAR441236, which was manufactured by Sanofi, has been designed to attach to three parts of the virus at the same time and to neutralize (or block) the ability of the virus to infect more cells. In research tests, SAR441236 attached to and disabled many strains of HIV.

The goal of treating people who are living with HIV is to reduce the amount of HIV in the blood (this is also known as "viral load") to undetectable levels. HIV is considered "undetectable" when the virus cannot be found (or detected) in your blood using a standard, clinical, FDA-approved viral load test.

In this study, for people who have already been taking ART and who have an undetectable viral load by FDA-approved tests, the study team will use a more sensitive research viral load test known as a "single copy assay." This test measures extremely low viral loads, even when the clinical viral load is undetectable. In this way, the study team will be able to investigate if SAR441236 can reduce your viral load even when it is already very low.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide to take part in this research study, you will be asked to sign and date this consent form and schedule a screening visit to determine if you can join the study. The screening visit will occur before you have any study-related procedures and before you are given any study treatment. If you are currently taking ART and you can join the study, you will have one more visit (a pre-entry visit for a blood collection) before the study starts. **At the screening visit, you will have a complete physical exam, you will be asked questions about your medical history and about drugs you have taken in the past and are taking now. You will have some blood and, possibly, some urine collected for testing to see if you are eligible for the study.**

<u>If you do not enroll into the study</u>
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, sex, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, $CD4^+$ T cell count [the number of white blood cells that fight infection], viral load) information will be collected from you to help ACTG researchers study whether there are patterns or common reasons why people do not join a study.

<u>Study treatment groups</u>
In this study, we plan to test several doses of SAR441236 one at a time. The doses will be tested in categories that we will refer to as Arm A, Arm B, and Arm C. If you are currently taking ART, you will be in Arm A or Arm C. If you have not started ART or if you have not taken ART for at least the past **8 weeks**, you will be in Arm B. In each arm, there will be a separate Dosing Group for each dose of SAR441236 that we are testing. You will only be in one Dosing Group and the dose that you receive will depend on when you join the study.

Within Arm A, the study team checked to see that a lower dose was safe before opening the next higher Dosing Group for enrollment. For added safety, in Arm A and in the first Dosing Group in Arm B, only two participants were allowed to receive study treatment at the same dose on a single day. After the first two participants received study treatment, and the study sites confirmed that there had been no serious side effects, the rest of the participants were permitted to enroll at the rate of up to two per day per Dosing Group. In Arm C, no more than two participants will be permitted to receive study treatment within a single week.

Beginning with this version **(Version 4.0)** of the study, **there will be up to three** dosing **groups** in Arm B. **One of these groups (Dosing Group 5) has already been completed.** Dosing Group 8 **opened to enrollment under the previous version of the protocol. It is possible that Dosing Group 7 will be opened to enrollment sometime after Dosing Grop 8 is fully enrolled. For more information,** see below, under "Arm B:"

Arm A: **(NOTE: Enrollment to this arm has been completed.)**
You will be in Arm A of the study if you have been taking ART for at least 12 months before you enter the study and that ART has kept HIV undetectable. You will continue to take your ART throughout the study.

There are four Dosing Groups in Arm A. You and your study doctor will be told which Dosing Group you are assigned to.

On the day you enter the study, you will be randomly assigned, as if by rolling dice, to receive either:
- SAR441236 or placebo.

Neither you nor your study doctor will be able to choose whether you will be assigned to receive SAR441236 or placebo. No matter which Arm A Dosing Group you are assigned to, it is twice as likely that you will be assigned to receive SAR441236 than placebo. A placebo is not an active drug and is not expected to have any effect. Neither you nor your study doctor will be told if you are assigned to receive SAR441236 or placebo.

The four Arm A Dosing Groups are:
- Dosing Group 1 (six participants): four participants will receive 1 mg/kg SAR441236 and two participants will receive placebo**.** This group was fully enrolled and all participants have completed their follow-up visits.
- Dosing Group 2 (six participants): four participants will receive 3 mg/kg SAR441236 and two participants will receive placebo**.** This group was fully enrolled and all participants have completed their follow-up visits.
- Dosing Group 3 (six participants): four participants will receive 10 mg/kg SAR441236 and two participants will receive placebo**.** This group was fully enrolled; some participants may still be having their follow-up visits.
- Dosing Group 4 (12 participants): eight participants will receive 30 mg/kg SAR441236 and four participants will receive placebo**.** This group was opened under the previous version and some participants are still having their follow-up visits. Enrollment to this group may continue.

If you were in Dosing Group 1, 2, or 3, you only received study treatment once at the beginning of the study. If you are in Dosing Group 4, you will receive four **infusions,** once at the beginning of the study and then three more times. **There will be about 12 weeks between infusions.**

Arm B:
You will be in Arm B if you **have not ever taken** ART or have not taken ART for at least **8 weeks** before entering the study. You should be able and willing to start or re-start ART by week **2** of the study. You must not have used the drugs listed below and you will not be permitted to include any of them in your ART regimen while you are on study. This is because it is not known whether taking SAR441236 might make these drugs less effective.

- Maraviroc (also known as Selzentry)
- Ibalizumab (also known as Trogarzo)
- Enfuvirtide (also known as Fuzeon or T-20)
- **Long-acting cabotegravir for at least 1 year before you enter this study**

The **three possible** Arm B Dosing Groups are listed below.
- Dosing Group 5 (six participants): 1 mg/kg SAR441236**.** This group **has completed follow-up.**
- Dosing Group 8 (six participants): 30 mg/kg SAR441236. **This group opened to enrollment in the previous version of the protocol. Note that t**he 30 mg/kg dose is the highest dose that was tested in participants in Arm A. Along with all the other doses tested in Arm A, it was found to be safe.
- Dosing Group 7 (six participants): 10 m/kg SAR441236. **Opening of this dosing group to enrollment will be dependent on information learned from Dosing Group 8.**

You will only receive study treatment once at the beginning of the study.

In Arm B, you will receive SAR441236. You will NOT receive placebo.

Note that taking SAR441236 before starting or re-starting ART is not standard practice. Standard practice is to start ART as soon as possible after finding out that you have HIV. If you had taken ART before, standard practice is to stay on it. If you stopped it, standard practice is to re-start ART as soon as possible. Based on information from recent studies comparing early and later ART start or re-start times, delaying ART for up to **2** weeks after you enter the study is not expected to increase your risk of complications from HIV.

Information about how SAR441236 affects HIV in people who have not started ART or who have interrupted ART could be used to help design future studies with **other drugs like** this drug.

Arm C: **(NOTE: Enrollment to this arm has been completed.)**
You will be in Arm C of the study if you have been taking ART for at least 12 months before the study starts and the ART has kept HIV undetectable. You will continue to take your ART throughout the study.

On the day you enter the study, you will be randomly assigned, as if by rolling dice, to receive either:
- SAR441236 or placebo.

A placebo is not an active drug, so it is not expected to have any effect.

It is twice as likely that you will receive SAR441236 rather than placebo. Neither you nor your study doctor will be told or will be able to choose whether you receive SAR441236 or placebo.

The two Arm C Dosing Groups are:
- Dosing Group 10 (six participants): four participants will receive 0.3 mg/kg SAR441236 and two participants will receive placebo
- Dosing Group 11 (six participants): four participants will receive 1 mg/kg SAR441236 and two participants will receive placebo

You will only receive study treatment once at the beginning of the study. The Dosing Group that you are in will depend on when you join the study.

Study Treatment
Study treatment for participants in Arm A or Arm C is either SAR441236 or placebo. Study treatment for participants in Arm B is SAR441236. Study treatment will be provided through the study.

If you are in Arm A or Arm B, study treatment will be given to you by infusion in your arm. An infusion is an injection that is delivered directly into a vein over a longer period of time than is typical for most injections. Depending on which Dosing Group you are in, the infusion will take either 30 to 60 minutes or 60 to 90 minutes. If there are any problems during the infusion, the clinic staff may interrupt the infusion or could slow the rate of the infusion. In these cases, if it is safe and possible for infusion to be completed, then it must be completed within 3 hours of when it started. **Your vital signs will be checked and you will be monitored for any side effects for 15 minutes after the infusion.**

If you are in Arm C, study treatment will be given to you by an injection under the skin (subcutaneous) in your abdomen. Depending on which Dosing Group you are in, you might receive one, two or three injections. It should take 5 to 15 minutes for you to receive the injection/s. If there are any problems during the injections, the clinic staff may interrupt the injections or might stop them. If it is safe and possible for the injections to be completed, they must be completed within 3 hours of when they started.

Doses
The doses that will be tested are listed above, by Arm and Dosing Group. In this list, “mg/kg” means that the amount of study drug in your infusion will depend not only on the group that you are in, but also on your weight. For example, if you are in one of the “3 mg/kg” groups and you weigh 75 kg (or about 165 lbs), the total amount of SAR441236 that you receive will be 225 mg (3 mg x 75 kg = 225 mg); if you are in one of the “1 mg/kg” groups and you weigh 75 kg (or about 165 lbs), the total amount of SAR441236 that you receive will be 75 mg (1 mg x 75 kg = 75 mg).

All participants will be required to take ART, either starting before study entry or within **2** weeks **after** starting the study. ART will NOT be provided through the study.

Study Visits
In this study, you will be seen in the clinic most days for the first week, then a few more times over the next 3 months, and then once more about 6 months from when you entered the study. **At all study visits you will have a physical exam.** If you are in Dosing Group 4, you will have four infusions, and **then** will have more visits **for about 9 months after your last infusion**.

If you are in Dosing Groups 1, 2, 3, 5, **7, or** 8, blood will be collected from you six different times over approximately 10 hours on the day that you receive study treatment. If you are in Dosing Groups 10 or 11, blood will be collected from you three different times over approximately 10 hours on the day that you receive study treatment. In all groups, blood will also be collected from you 24 hours (1 day) after you receive study treatment. You may be asked to stay overnight at a clinic facility during this time. Blood will also be collected from you one time at each of the remaining study visits. Some of this blood will be used to study levels of study treatment over time**, some will be used for safety tests, and some will be used or stored for study-required testing**. **At some visits, you will be asked to provide a urine sample.**

If you are in Dosing Group 4, a small amount of blood will be collected from you at the times listed below. Some of this blood will be used to study levels of study treatment over time.

- Six different times over approximately 10 hours on the day that you receive your 1st infusion of study treatment
- 24 hours (1 day) after the 1st infusions ends. You may be asked to stay overnight at a clinic facility during this time.
- One time at each study visit until you have your 2nd infusion
- Before the infusion on the day that you have your 2nd infusion
- 2 days after your 2nd infusion
- One time at each of the other study visits between your 2nd and 3rd infusions
- Before the infusion on the day that you have your 3rd infusion
- 2 days after your 3rd infusion
- One time at each of the other study visits between your 3rd and 4th infusions
- Six different times over approximately 10 hours on the day that you have your 4th infusion
- 24 hours (1 day) after your 4th infusion ends. You may be asked to stay overnight at a clinic facility during this time.
- 2 days after your 4th infusion
- One time at each of the remaining study visits

<u>All dosing groups</u>
If you are unable to come to the clinic **according to the study schedule (for example,** because of **concern about exposure to** illness**,** the site is unable to conduct non-essential study visits**)**, then some of your scheduled study visits may be conducted remotely (for example, by telephone or telehealth) **or may be postponed until they can be conducted in the clinic**. **If you are in Group 4, if any infusion visits are postponed, your time on study will be extended so that you can be followed for approximately 9 months after your last infusion.**

<u>Leaving the study early</u>
If you have to leave the study early, you may be asked to come in for one final visit before ending your participation in the study.

<u>Vaccinations</u>
Because vaccinations activate your immune system, you must agree not to receive any vaccination within 30 days before entering the study or within **30 days** after receiving a study drug. The study team **will permit administration** the flu **and/or SARS-CoV-2 (COVID-19)** vaccine **if they are notified in**

advance. If you need to receive a vaccination at any other time on study, you will have to get the vaccination at least 30 days before **or after** a scheduled study **drug administration**.

Some of the blood that is collected from you will be used to check the levels of SAR441236 and anti-HIV medications in your blood.

You will not receive the results from these tests.

MAY I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used for study-required testing, including testing the levels of SAR441236 and of anti-HIV medications in the blood; immunologic, and virologic testing. Some genetic testing of the virus (HIV) will also be performed.

Your samples and any private information that has been collected about you **will be coded**. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

Please refer to Attachment A to consider providing consent for use of your blood in other studies.

Please note that as a research participant, you have the option of withdrawing your consent at any time for the storage or future use of samples that have been collected from you.

WILL I RECEIVE THE RESULTS OF ANY TESTS?

You will receive the results of routine lab tests (for example, blood counts, liver and kidney tests, viral load, CD4 count) that are performed at the study visits. You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your care, you will be provided with those results.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 53 and 65 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

People who receive just one administration of study treatment will be in the study for about 24 weeks (about 6 months). If you are in Arm A, Dosing Group 4, you will be in the study for about **9 months after**

your last infusion. If you are able to have all four of your infusions about 12 weeks apart, then your total time on study will be about 18 months, which is about a year and a half.

WHY WOULD THE STUDY DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- You do not receive any study treatment
- Your study doctor or regular doctor thinks the study is no longer in your best interest
- continuing the study treatment may be harmful to you
- You are not able to attend study visits as required by the study
  - Note that this does not apply if the study visits **can be** conducted remotely **or have been postponed**
- Your clinic site is no longer funded through the ACTG
- The study is cancelled
- You request to stop participating

In some cases, you will be asked to stay on study and continue to attend study visits through 12 weeks after you last received study treatment. You will then have one final discontinuation visit before leaving the study.

The study doctor may also need to take you off the study treatment without your permission if:
- You become pregnant
- You are breastfeeding
- You have a bad reaction to the study drug
- You are being treated with certain medications (the study staff will discuss these with you prior to giving you study treatment)

WHAT HAPPENS IF I HAVE TO STOP TAKING STUDY TREATMENT EARLY?

<u>During the study</u>
You will be asked to remain on study for at least 12 weeks for safety follow-up. You will have one final discontinuation visit before leaving the study.

<u>After the study</u>
SAR441236 will not be available to you after you have completed your study participation; its use in humans is still being studied.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this study drug. This list includes the more serious or common side effects with a known or possible relationship. If you have questions concerning the

additional study drug side effects, please ask the study staff at your site. If you experience any side effects at any time while you are on study, contact the study staff at your study site.

There is a risk of serious and/or life-threatening side effects when non-study drugs are taken with the study drug. For your safety, you must tell the study doctor or study nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or study nurse before enrolling in any other clinical trials while on this study.

Risk of SAR441236

SAR441236 has not been tested in humans. With antibody products, side effects may occur within the first 24 hours or after several days or weeks. There may be a risk of serious allergic reactions, which can be life-threatening.

- Anaphylaxis is one type of allergic reaction that may occur soon after an antibody product is given. It includes:
  - Difficulty breathing
  - Low blood pressure
  - Hives or rash
  - Swelling in the mouth and on the face.
- Serum sickness is a delayed type of allergic reaction that may occur several days to 3 weeks after an antibody product is given. It is characterized by:
  - Hives or rash
  - Fever
  - Enlarged lymph nodes
  - Muscle pain
  - Joint pain or swelling
  - Chest discomfort
  - Shortness of breath.
- You may also experience an increase in liver enzymes, a blood test that can be a sign of liver damage.

Antibody products for which serious allergic reactions have been observed are either targeted to attack a human protein or they have a structure that is somewhat like an animal antibody. There may be a lower risk of serious allergic reactions with SAR441236 because SAR441236 is a partially human antibody that attacks a virus.

Some antibodies of the type that attack human proteins increase the risk of serious infections. SAR441236 is not expected to increase the risk of serious infections because, as noted above, it attacks a virus rather than a protein.

It is possible that SAR441236 will have unknown effects, such as changes in CD4 cell count or viral load levels, changes in how well individual anti-HIV medications can control HIV in your blood, or other unknown effects. In addition to the possible risks that are listed above, SAR441236 may have other side effects that we do not know about. Participation in this study may limit your eligibility for other future monoclonal antibody studies.

In a recent study in participants without HIV, injection site reactions were seen when an antibody was injected under the skin (subcutaneously - the way it will be in Arm C Dosing Groups 10 and 11). One person had a serious injection site reaction. The antibody used in that study binds to the same target that part of SAR441236 does but it is not the same antibody as in SAR441236. The serious reaction included a rash and flu-like symptoms. It is not unusual for drugs (including antibodies) that are injected under the skin to cause reactions at the injection site. When the same drugs are injected into a vein (the way that SAR441236 will be in in two study arms in this study), they usually do not cause the same kind of reaction. The study drug that caused the reactions in the other study was injected under the skin and not into a vein.

Participants in A5377 will be observed carefully and checked for side effects during the infusion of SAR441236 (or placebo). Observations and checks for side effects will be made multiple times over the first 2 to 10 hours after the infusion or SC injection, and then again at every visit for the first 2 weeks after the infusion or SC injection.

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

In addition to the side effects listed above, other side effects may include:
- Pain
- Headache
- Fever
- Nausea and vomiting
- Dizziness
- Trouble breathing
- Shortness of breath
- Tiredness
- Tightening of the muscles around the bronchial tubes (or airway)
- Change in blood pressure (low/high)
- Chills
- Diarrhea
- Itchiness
- Rash
- Hives
- Swelling (lip or face)
- Increased heart rate or chest pain
- Fainting may occur after receiving the infusion, which may result in falling and injury
- Shaking
- Muscle cramps
- Seizure-like activity has also been reported

<u>Risks of Infusion</u>
In addition to risks related to the study drug, there are some risks related to the infusion that might happen at the infusion site (where the needle goes into your arm). These include:
- Pain or tenderness

- Swelling
- Redness
- Bruising
- Itching

Risks of Subcutaneous Injection
In addition to risks related to the study drug, there are some risks related to the subcutaneous injection that might happen at the injection site (where the needle goes into your skin). These include:
- Pain or tenderness
- Swelling
- Redness
- Bruising
- Itching

Risks of Social Harm
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that your involvement in the study as a participant could become known to others, if it is not already, and that social harm may result (because you could become labeled as someone with HIV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community.

ARE THERE RISKS RELATED TO PREGNANCY?

SAR441236 is not approved for use in pregnant **individuals** and may be unsafe for unborn babies.

If you are having sex that could lead to pregnancy, you must agree not to become pregnant or to attempt to make **another person** pregnant.

You must also agree not to participate in an assisted conception process (such as sperm donation, intrauterine insemination or in vitro fertilization) from screening until 12 weeks after the final study visit.

If you are having sex that could lead to pregnancy, you must agree to use at least one of the approved methods listed below to prevent pregnancy from study entry until 12 weeks after your last study visit.
- Birth control medications that prevent pregnancy and that are given as pills or shots, or placed on or under the skin
- 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

If you are interested in starting a form of birth control, please talk with study staff about how you can obtain your desired choice of birth control.

If you are able to become pregnant, you must have a **blood or urine** pregnancy test before any dose of SAR441236. The test must show that you are not pregnant.

If you think you may be pregnant at any time or if you begin breastfeeding during the study, you must tell the study staff right away. The study staff will talk to you about your choices. If you are pregnant or breastfeeding, you will discontinue study drug. This means that if you are in Group 4 and you have not had all four infusions by the time you discover that you are pregnant or begin breastfeeding, you will not be given any more study treatment. Study site staff will ask to contact you regarding your pregnancy. We will collect information about you and about the delivery and health of your baby (even if your participation in the study has ended). You will be asked to stay on study at least 12 weeks after you stop study drug for safety evaluations. If possible, the study team would prefer that you stay on study for safety evaluations until the end of the study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there will be no direct benefit to you. The information learned from this study may help others with HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

You can choose not to be in this study, continue with your normal medication regimen or start a new regimen, and be followed by your regular doctor or health care provider.

Please talk to your study doctor about this and other choices available to you. Your study doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and non-US regulatory entities, Advarra Institutional Review Board (IRB) (a committee that protects the rights and safety of participants in research), the National Institutes of Health (NIH), study staff, study monitors, and the drug company supporting this study or its designee, as part of their duties. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

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

WHAT ARE THE COSTS TO ME?

There will be no cost to you for any of the tests that you have as part of this study. ART will NOT be provided through the study, and you or your insurance company will be responsible for its cost. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE PAYMENT?

«Compensation»
You will not receive payment, but you will be reimbursed for some of your time and expenses. You will receive a total of *($XXX [$250 is recommended by the study team])* on the day*/days* that you are asked to have multiple blood collections over an entire day. This money will be given to you to compensate you for some of your time and some of your transportation or other expenses on this*/these* day*/days*. For most participants, this will only occur once, on the day of the infusion. For participants in Arm A, Group 4, this will occur twice, on the day of the first infusion and then again on the day of the fourth infusion.

[If applicable:] We will reimburse you for the cost *of* ***[describe: e.g., traveling to your study visits]***. You will be reimbursed approximately ***[e.g., 2 weeks, 1 month****, etc.]* after you submit your travel receipts to the study staff.

WHAT HAPPENS IF I AM INJURED?

If you become ill or are injured while you are in the study, get the medical care that you need right away. You should inform the healthcare professional treating you that you are participating in this study. If you tell the study staff that you think you have been injured then they will help you get the care you need.

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing and dating this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. Whether or not you participate in this study will not affect your medical care at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact**:**

By mail:
Study Subject Adviser
Advarra IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046
or call **toll free**: 877-992-4724
or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00041224.

SIGNATURE PAGE

If you have read this consent form all your questions have been answered, and you agree to take part in this study, please sign your name below and **write in the** date.

Participant's Name (print)	Participant's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date

ATTACHMENT A: CONSENT FOR USE OF YOUR EXTRA SAMPLES FROM A5377

Blood that is collected from you as part of A5377 will be stored in vials (which will be referred to as "samples"). If there are samples left over after all A5377-related research has been done, the ACTG may want to use them or share them with other researchers. These samples are called "extra samples". The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask the study staff at your study site.

Your samples and any private information that has been collected about you **will be coded**. This means that no one looking at the labels or at other information will know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored.

When researchers want to use your samples and information, their research plans must be approved by the ACTG. Each researcher's institutional review board (IRB) will need to review the plans. IRBs protect the rights and well-being of people in research. If research plans are approved, the ACTG will send your samples and/or information to the researchers' location or designated facility. This means that researchers who are not part of the protocol team may use your samples or information without asking you again for your consent.

You will not be paid for your samples or information. A researcher may make a new scientific discovery or product based on the use of your samples or information. If this happens, there is no plan to share any money with you.

You may withdraw your consent for research on your extra samples or information at any time. If you do this, any unused samples will be discarded and no further sharing of your information will be permitted.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the study staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples and information

OR

____ (initials) I understand but I do not agree to this storage and possible use of my samples or information

Research with Human Genetic Testing

Your study site might ask if you would like to participate in A5128 (Plan for Obtaining Informed Consent to Use Stored Human Biological Materials [HBM] for Currently Unspecified Analyses), the ACTG study that collects blood and/or saliva specifically for genetic testing. If you would like to participate in A5128, you will sign and date a separate consent form for that study. Your extra samples from A5377 will not be used for human genetic testing **unless you sign and date the consent form for A5128**.

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

Your name
Address
Phone number
Date of birth
Medical history
Information from your study visits, including all test results.

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- Representatives of National Institutes of Health, National Institute of Allergy and Infectious Diseases, and AIDS Clinical Trials Group.
- Representatives of University of California, Los Angeles.
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study).
- The Food and Drug Administration (FDA) and other US federal and state agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.
- Governmental agencies of other countries.
- Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.
- Other research doctors and medical centers participating in this study.
- A data safety monitoring board which oversees this study.

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study drug works and is safe.
- To compare the study drug to other drugs.
- For other research activities related to the study drug.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____

_____

Participant's Name (print) Participant's Signature and Date

_____

Study Staff Conducting Authorization Discussion (print) Study Staff's Signature and Date