Approvals

ACTG A5377

Primary Statistical Analysis Plan

Version 4.0

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

Protocol Version 4.0

ClinicalTrials.gov Identifier: NCT03705169

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This is the ACTG A5377 SAP Version 4.0 with names of authors, names of publication writing team members, and analysis timelines redacted.

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Version History

Version	Changes Made	Date Finalized
1	Original Version	3/18/2019
1.1	Letter of amendment review (V2.0, LOA #1) by [redacted]	10/11/2019
2.0	Updated to accommodate changes in Protocol Version 3.0 and LOA #1. Formatting changes undertaken to provide consistency with the most recent template.	12/07/2020
2.1	The SAP was reviewed in light of Protocol Version 3.0, LOA #2 and it was determined no changes were needed.	3/10/2021
3.0	The SAP was reviewed in light of Protocol Version 4.0 and minor changes were made throughout. The detailed visit window table was removed and added to the primary AIP.	11/14/2022
4.0	**Changes made to accommodate modifications in PK analysis as the result of never opening Arm B Cohort 7 (10 mg/kg) and limited enrollment in Arm B Cohorts 5 (1 mg/kg) and 8 (30 mg/kg). Changes are bolded.**	**October 23, 2023**

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures of the ACTG A5377 study that will be included in the primary manuscript(s), and which address, at a minimum, the primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov. This document corresponds to A5377 Protocol Version 4.0.

The SAP outlines the outcome measures and statistical principles for all parts of the primary analysis report. These may be modified as new information becomes available or to reflect recommendations of the Safety Monitoring Committee (SMC).

Detailed outlines of tables, listings, and figures that will be included in the primary analysis report are included in the Analysis Implementation Plan (AIP). The AIP will also provide specific coding details, data sources, and validation requirements.

1.2 Version History

In Version 1.1, [redacted] reviewed the SAP in light of LOA #1. No substantive changes were required.

In Version 2.0, changes were made to accommodate Version 3.0 of the protocol. These changes include the addition of a subcutaneous injection arm (Arm C, Cohorts 10 and 11) and dose de-escalation design in Arm B. A COVID-19 specific appendix was also added. Changes from Version 1.0 are shown in red.

In Version 2.1, [redacted] reviewed the SAP in light of Version 3.0, LOA #2. No substantive changes were required.

In Version 3.0, [redacted] reviewed the SAP in light of Version 4.0 of the protocol. No substantive changes were required but minor modifications were made throughout (and are bolded). The visit window section (4.1) was clarified and the corresponding tables (Table 1 and 2) were removed and added to the primary AIP where they were further edited for clarity (and to capture instances where multiple samples were obtained during a single visit [e.g., intensive PK and HIV-1 RNA]).

In Version 4.0, the SAP was reviewed in light of the closing of the study without opening Arm B Cohort 7 (10 mg/kg) and limited enrollment into Arm B Cohorts 5 (1 mg/kg) and 8 (30 mg/kg). Changes were made to the planned PK analyses (primary and secondary) as well as some secondary efficacy analyses. Changes are bold.

2 Study Overview

2.1 Study Design

A5377 is a phase 1, first-in-human study of SAR441236. It will include three arms with multiple cohorts in each arm.

2.2 Regimen

Double-blind randomization in Arms A and C will be 2:1 SAR441236:placebo. Arm B participants will all receive open-label SAR441236.

Arm A (Treated, virologically suppressed)

- Cohort 1: 1 mg/kg of SAR441236 or saline placebo administered as a single intravenous (IV) infusion. Cohort 1 enrollment was completed under Protocol 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 Protocol 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 Protocol 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 **began** under Protocol Version 2.0 **and completed under Protocol Version 3.0**.

Arm B (HIV viremic)

- Cohort 5: 1 mg/kg of SAR441236 administered as a single IV infusion. **Cohort 5 enrollment began under Protocol Version 2.0 and was closed with Protocol Version 3.0.**
- Cohort 7: 10 mg/kg of SAR441236 administered as a single IV infusion. **Cohort 7 never opened to enrollment.**
- Cohort 8: 30 mg/kg of SAR441236 administered as a single IV infusion. **Cohort 8 enrollment began under Protocol Version 3.0. No additional participants enrolled under Protocol Version 4.0.**

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

Arm C (ART-treated, virologically suppressed)

- 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.

Figure 1: Schema Arm A

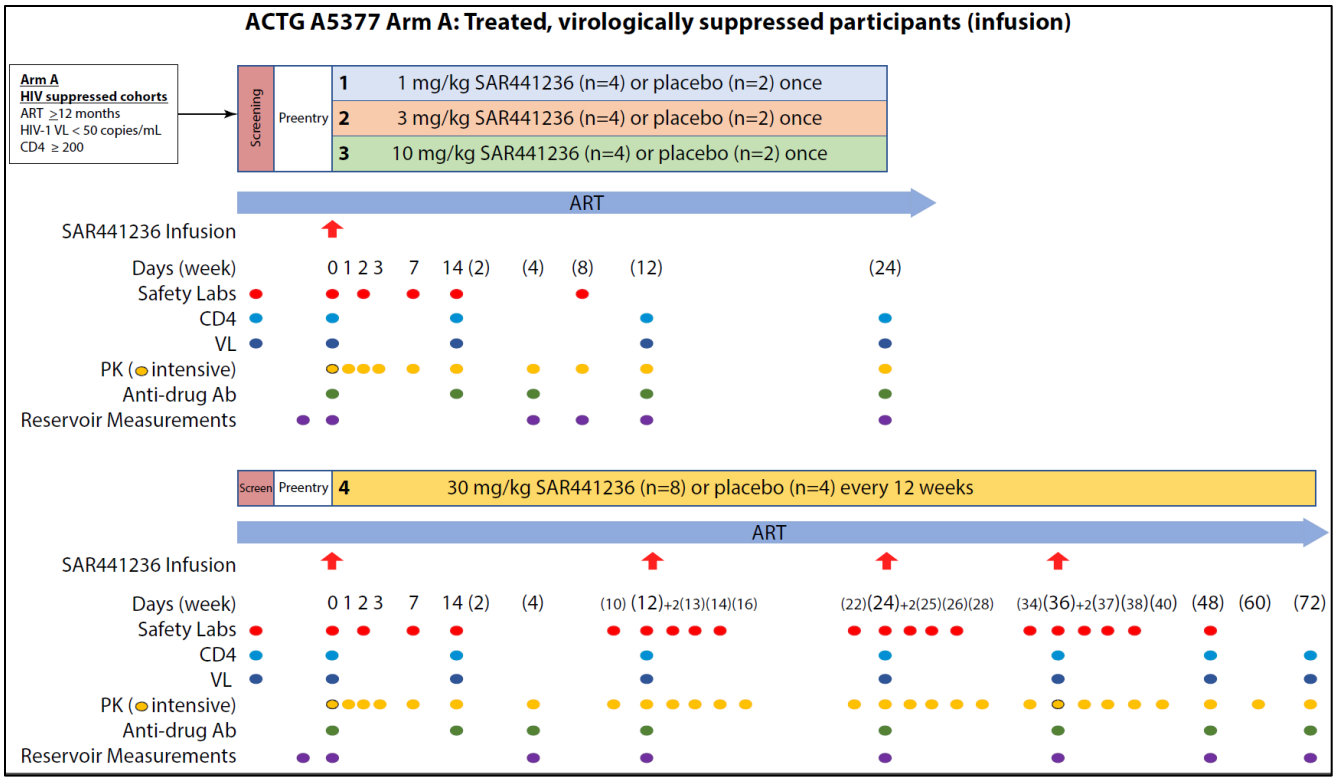


Figure 2: Schema Arm B

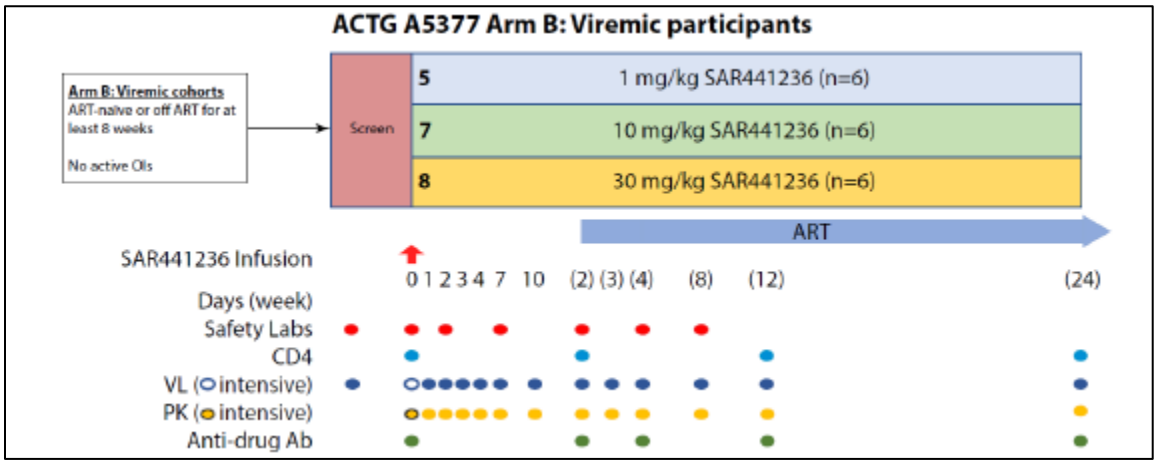
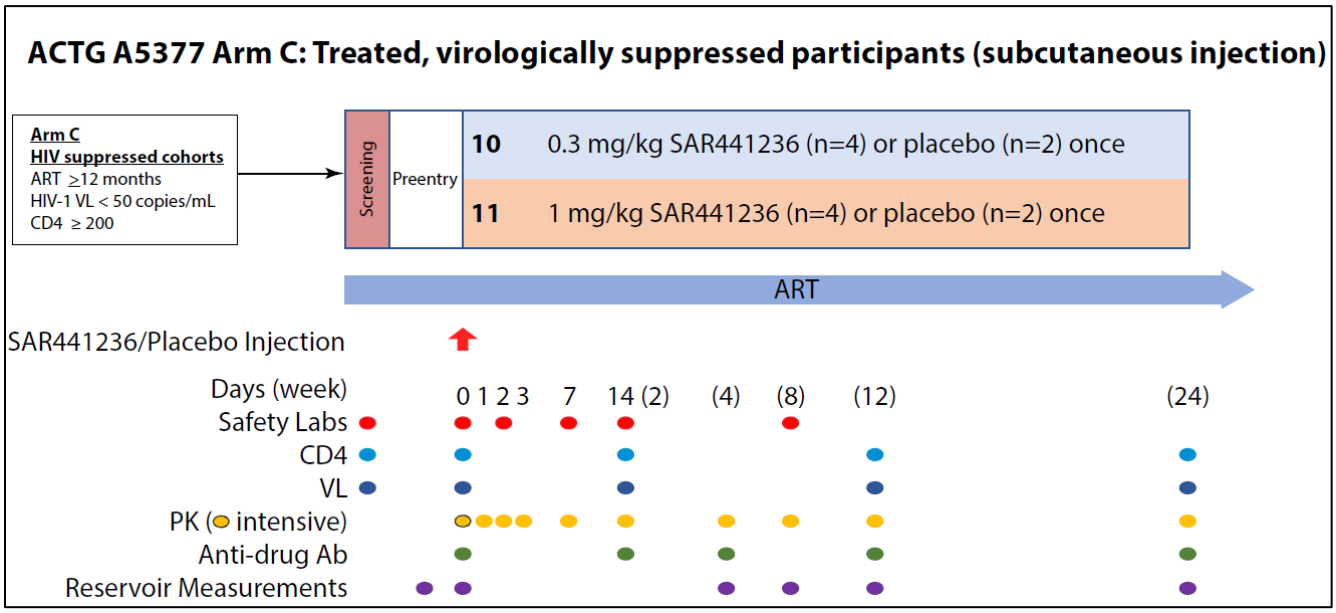


Figure 3. Schema Arm C



2.3 Hypotheses

1. Infusion of SAR441236 is safe and well tolerated at the proposed doses.
2. The pharmacokinetics (PK) of SAR441236 after infusion of a single dose is similar in viremic and virologically suppressed participants with HIV.
3. SAR441236 has dose-dependent anti-HIV-1 activity in viremic participants with HIV.
4. Subcutaneous injection of SAR441236 is safe and well tolerated at the proposed doses.

2.4 Study Objectives

This Primary SAP addresses the primary and secondary objectives listed in the study protocol. The primary PK outcome estimates will be generated outside of the SDAC by the protocol pharmacologist and their estimation procedure and analyses will be defined in a separate document. The remaining study objectives listed in the protocol will be addressed in subsequent analysis plans.

2.4.1 Primary Objectives

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).
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).

3. To evaluate the antiviral activity of a single dose of SAR441235 in viremic participants with HIV at Day 7 after the infusion (Arm B).

2.4.2 Secondary Objectives

1. To evaluate the dynamics of plasma HIV-1 RNA decay in viremic participants receiving SAR441236 (Arm B).
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).
3. To evaluate if anti-SAR441236 antibodies are induced after single or multiple doses.
4. To evaluate the effects of single and multiple doses of SAR441236 on CD4+ T-cell counts.
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.

2.5 Overview of Sample Size Considerations

The total sample size of this study is **53-65** evaluable participants (**39-51** active-treated participants and 14 placebo participants). In Arms A and C, the proposed sample size provides a reasonably high probability of dose escalation when the true event rates are in fact acceptable, as well as providing low probability of dose escalation when the true event rates are unacceptable. In Arm B, the proposed sample sizes and dose de-escalation scheme (described in Protocol Section 10.4.2) provide a reasonably high probability of dose de-escalation when the true response rate (i.e., HIV-1 RNA reduction of at least 1.0 $\log_{10}$ copies/mL from baseline by Day 14) for a given dose cohort is high.

For the primary outcome measure of efficacy in Arm B, 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.

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 **OR. Beginning with Version 4.0 of the protocol, have an entry plasma HIV-1 RNA <5000 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.

2.6 Overview of Formal Interim Monitoring

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 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 participants experience a Grade ≥3 AE that is definitely related to study treatment or that is Grade ≥4 that is probably or possibly related to study treatment (as judged by the CST, blinded to active/placebo treatment) or
d. One or more participants experience 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 each of Cohorts 5-8, efficacy data will be reviewed by the CST (see Protocol Section 10.4.2) to determine whether to dose de-escalate. This is described in more detail below.

2.6.1 Efficacy Analysis for Dose De-Escalation

Virologic response by Day 14 for participants in Arm B cohorts will be assessed. 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 log10 copies/mL from baseline. With that definition, the dose de-escalation criteria for an Arm B cohort are:

a. At least 3 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.

Evaluation of Arm B cohorts will not be impacted by this interim efficacy look.

3 Outcome Measures

3.1 Primary Outcome Measures

Per protocol section 10.2.1, the primary outcome measures are as follows:

3.1.1 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).

3.1.2 Pharmacokinetics

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

3.1.3 Efficacy

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 of monotherapy for viremic participants with HIV (Arm B cohorts).

3.2 Secondary Outcome Measures

Per protocol section 10.2.2, the secondary outcome measures are as follows:

1. Plasma HIV-1 RNA (copies/mL) at baseline and post-infusion for viremic participants with HIV (Arm B Cohorts).
2. Change in plasma HIV-1 RNA (log10 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).
3. Attributions of anti-SAR441236 antibodies in all cohorts.
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 (cell/mm^3) from baseline to week 12 following each infusion for Cohort 4.
5. Pharmacokinetic parameters (see protocol section 11.0) of SAR441236 following each infusion or SC injection.
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.

4 Statistical Principles

4.1 General Considerations

4.1.1 Analysis populations

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, will be replaced to ensure enough safety data are available for dose escalation evaluation. Arm B participants who discontinue the study prior to Day 14 without sufficient virology (as judged by the CST) **or have HIV-1 RNA < 5000 copies/mL at study entry** 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 encouraged to remain on study and complete all study follow-up.

Safety population: All participants who have been exposed to SAR441236 or placebo.

Efficacy population: In by-cohort analyses, all participants who actually receive ≥**0.9 mg/kg SAR441236 and have an entry plasma HIV-1 RNA ≥ 5000 copies/mL**. These participants should have efficacy measures that are sufficient and interpretable.

PK population: All participants who have been exposed to SAR441236 and have evaluable levels of SAR441236 such that PK parameters can be derived.

4.1.2 Times used in the Primary and Secondary Outcome Definitions

For Cohorts 1-3 and 10-11 (Arms A and C) evaluations will occur on the infusion day (Day 0) prior to the infusion and at hours 0, 2, 4, 6, and 10 (± 15 min) post infusion. Additional follow-up will occur at Day 1 (± 4 hrs), 2 (± 8 hrs), and 3 (± 12 hrs) and at Weeks 1 (± 1 day), 2 (± 2 days), 4 (± 2 days), 8 (± 7 days), 12 (± 7 days), and 24 (± 7 days).

For Cohorts 5-8 (Arm B) evaluations will occur on the infusion day (Day 0) prior to the infusion and at hours 0, 2, 4, 6, and 10 (± 15 min) post infusion. Additional follow-up will occur at Day 1 (± 4 hrs), 2 (± 8 hrs), 3 (± 12 hrs), 4 (± 12 hrs), 7 (± 1 day), and 10 (± 1 day) and at Weeks 2 (± 2 days), 3 (± 2 days), 4 (± 2 days), 8 (± 7 days), 12 (± 7 days), and 24 (± 7 days).

For Cohort 4 (Arm A), evaluations will occur on the first infusion day (Day R) prior to the infusion and at hours 0, 2, 4, 6, and 10 (± 15 min) post-infusion. Additional first infusion follow-up will occur at Day 1 (± 4 hrs), 2 (± 8 hrs), and 3 (± 12 hrs) and Weeks 1 (± 1 day), 2 (± 2 days), 4 (± 2 days), and 10 (± 7 days). The R + Wk 10 visit may be repeated if the subsequent infusion is delayed.

For the second and third infusions, evaluations will occur on the infusion day (Day R) prior to the infusion only. Additional second and third infusion follow-up will occur at Day 2 (as indicated) and Weeks 1 (± 1 day), 2 (± 2 days), 4 weeks (± 2 days), and 10 weeks (± 7 days). All of these firsts are relative to the last infusion, Day R. Again, the R + Wk 10 visit may be repeated if the subsequent infusion is delayed.

Per Protocol Version 2.0 CM #2 (March 24, 2020), Cohort 4 participants with infusion interruptions caused by the COVID-19 pandemic were referred to the Arm A, single dose SOE (Table 6.1-1) and thus may have additional visits at R + Week 12 (± 7 days) and R + Week 24 (± 7 days).

For the fourth, and final infusion, evaluations will occur on the infusion day (Day R) prior to the infusion and at hours 0, 2, 4, 6, and 10 (± 15 min) post-infusion. Additional fourth infusion follow-up will occur at Day 1 (± 4 hrs) and 2 (± 8 hrs), and Weeks 1 (± 1 day), 2 (± 2 days), 4 (± 2 days), 12 (± 7 days), 24 (± 7 days), and 36 (± 7 days).

The protocol windows described above will be expanded to create 'analysis windows. These analysis windows will be defined as non-overlapping intervals spanning approximately the entire period of follow-up, starting and ending halfway between each successive study visit for which a specified evaluation is expected. This decision was made to increase data availability at later follow-up time points with minimal impact to study results. If there are multiple evaluations within the window for a given visit, the evaluation closest to the definition of scheduled study week will be used.

4.2 Analysis Approaches

4.2.1 Analysis of Primary Objectives

Safety and tolerability

All Grade ≥3 AEs that are **at least possibly** related to study treatment (as judged by the core safety team, blinded to study treatment) any time from study treatment administration through the entire follow-up will be summarized. The primary safety outcome will be summarized as the percentage of participants experiencing the above defined AE with 2-sided 95% confidence interval using exact binomial methods, separately for the active treatment group of each cohort and for the combined placebo groups (Arms A and C only**).** All data gathered for Cohort 4 participants will be used when pooling placebo participants. The analysis will use the Safety population defined in section 4.1.1.

Details of each AE included as the primary safety outcome will be provided in listings: cohort, study treatment, event description, grade, lab value and units, days of event post first infusion, days of event post most recent infusion (Cohort 4 only), date of onset, date of resolution, and relationship to study treatment (as judged by the core safety team).

Similar listings will be provided for SAEs and AEs, regardless of grade, that were related to study treatment or procedure (as judged by the core safety team). In addition, all AEs reported any time from study treatment administration through the entire follow-up will be summarized for the active treatment group of each cohort and for the combined placebo groups (Arms A and C only).

Pharmacokinetics

AUC_{12Wk} for all cohorts will be summarized for the active treatment group by cohort in the PK population. The method for AUC estimation will be outlined in a separate PK plan. **Due to the limited sample size in Arm B, the pre-planned analyses using a linear regression model to estimate the mean difference between same dose cohorts in arm A vs. arm B is not feasible. AUC_{12WK} will be estimated for participants with sufficient data. For arm B participants, only descriptive statistics will be provided. The geometric mean ratio (and corresponding**

confidence interval) of dose-normalized AUC_{12Wk} (natural log transformed) will be estimated for Arm A vs. Arm C.

Sensitivity analysis including the active treatment subset of the Safety population as defined in Section 4.1.1 will be conducted.

Efficacy

For the primary efficacy analyses for Arm B cohorts, reduction in plasma HIV-1 RNA (log_{10} copies/mL) from baseline to Day 7 will be summarized, both in a combined cohort and in each cohort separately. The comparison between pre- and post-treatment will be carried out using a paired t-test with 2-sided 95% confidence interval for the combined cohort, and a Wilcoxon signed rank test for each cohort separately. The analyses will use the Efficacy population defined in Section 4.1.1. **Sensitivity analysis will be carried out using a Wilcoxon signed rank test for the combined cohort.**

Sensitivity analysis including the Safety population as defined in Section 4.1.1 will be conducted.

4.2.2 Analysis of Secondary Outcomes

- **Plasma HIV-1 RNA (log_{10} copies/mL) at baseline and post-infusion for treatment-naïve, viremic participants with HIV (Arm B cohorts)**

  Longitudinal participant-specific plots for antiviral activity before initiation of ART will be presented for each participant in Arm B. **Given the little evidence of viral decay in Cohort 5 and the limited sample size in Cohort 8 (n=2), the planned modelling for viral decay will not be not conducted.**

- **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 treatment-naïve, viremic participants with HIV (Arm B cohorts)**

  Similar analyses described in section 4.2.1 for the primary efficacy endpoint at Day 7 will be conducted for the Day 14 results. Summary statistics will be provided for the maximum reduction of each participant by dose cohort during monotherapy of SAR441236 (post-infusion and before ART initiation). **Protocol Version 4.0 considers the maximum reduction during 14 days of monotherapy because the timing for ART initiation/re-initiation was changed from "by 28 days" (Version 3.0 or earlier) to "at 14 days" for Arm B participants. However, since no participants enrolled under Version 4.0, we consider maximum reduction occurring in up to 28 days of monotherapy for Arm B participants.**

- **Attributions of anti-SAR441236 antibodies in all cohorts.**

The ADA status of participants exposed to anti-SAR441236 antibodies will be tabulated by scheduled visit day/week. Details of participants who developed anti-SAR441236 antibodies will be provided.

- **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.**

  Longitudinal participant-specific plots and numerical summaries for change from baseline in $CD4^+$ T-cell counts (cells/mm^3) will be presented by cohort.

- **Pharmacokinetic parameters of SAR441236 following each infusion.**

  Descriptive numerical summaries of the following PK parameters (protocol section 11.3) by dose cohort will be presented:

Single dose:	**Multi-Dose:**
• **Maximum concentration (C_{max})** • **Time of maximum concentration (T_{max})** • **Dose-normalized maximum concentration** • **Terminal half-life** • **Clearance (CL) for Arms A and B** • **Apparent clearance (CL/F) for Arm C** • **Volume of Distribution (V_d) for Arms A and B** • **Apparent volume of distribution (V_d/F) for Arm C**	• **Concentration 12-weeks after each infusion** • **AUC AI (12 Week Post Dose 1 vs Dose 4)** • **Trough AI (12 Week Post Dose 1 vs 4)** • **AUC 12-24WK** • **AUC 24-36 WK** • **AUC 36-48 WK** • **AUC 0 – 48 WK**

  These parameters, while different than those specified by the protocol, were calculated by the pharmacologist based on the available concentration data. Graphical approaches will display concentration curves over time. Please refer to the PK analysis plan for additional details **on the estimation of these parameters**.

- **Concentration (or dose)-response relationship between SAR441236 exposure and changes in plasma HIV-1 RNA from entry baseline to week 4 (or viral load nadir) (Arm B cohorts)**

  Longitudinal participant-specific plots of SAR441236 concentration and HIV-1 RNA (log_{10} copies/mL) over time will be presented. **Additionally, AUC vs change in HIV-1 RNA will also be plotted. If able to be calculated, d**escriptive summaries of EC_{80} and EC_{max} will be presented. Please refer to the PK analysis plan for additional details.

5 Report Contents

In addition to the tables, figures, and analysis results described above, the information in the following section will be included in the report. Additional details describing the presentation of this information can be found in the AIP.

5.1 Screening and Enrollment

- Number of participants screened
- Number of participants enrolled
- Reasons why participants did not enroll

5.2 Baseline Characteristics

Baseline characteristics summary tables will include, but not be limited to, the following:

- Sex
- Gender
- Participant reported race and ethnicity
- Age on the day of study entry
- IV drug use
- Baseline CD4+ count
- Baseline HIV-1 RNA
- Baseline weight and BMI
- ARV regimen taken at entry (Arms A and C only)

Note: Baseline measurements are any measurements taken prior to treatment initiation. If multiple measurements exist, the measurement taken closest to treatment initiation will be used.

5.3 Analysis Population

- Number of participants randomized
- Number of participants in the safety population
- Number of participants in the efficacy population
- Number of participants in the PK population

5.4 Study Status

- Protocol completion status: number of participants who completed protocol, number of participants off study prior to the protocol completion
- Time and reasons for participants off study prior to the protocol completion

5.5 Study Treatment Status

- SAR441236 infusion status (Cohort 1-3 and 10-11, first dose of Cohort 4, and Arm B): number of participants who never started the infusion, number of participants who initiated but did not complete the infusion, number of participants who completed the infusion. Reasons for participants who never started or did not complete infusion.
- SAR441236 infusion status (Cohort 4 only): number of participants who never started infusion, number of participants who did not complete all 4 infusions, number of participants who completed all 4 infusions, and the timing of each infusion. Reasons for participants who never started the infusion, did not complete all 4 infusions, or delayed infusion. Time of last infusion received.
- Actual dose infused for participants who only received partial dose of SAR441236 at each infusion.
- Duration of infusion.

5.6 Antiretroviral Therapy Status

- Time and regimen for ART initiation (Arm B only)
- ART modification and discontinuation.

5.7 Safety and Tolerability

- Primary safety outcome (Section 4.2.1)
- Other safety outcome:
    - Treatment- or procedure-related adverse events
    - Serious adverse events
    - Adverse events leading to treatment discontinuation
    - Summary of all adverse events
    - Targeted symptoms
    - Deaths

Note: Listing of all adverse events will be included in the appendix

5.8 Pregnancy

- Listings include details on pregnancy diagnoses: time, dose cohort, infusion status, pregnancy outcome

5.9 SAR441236 Pharmacokinetics

- Primary pharmacokinetic outcome (Section 4.2.1)
- Secondary pharmacokinetic outcomes (Section 4.2.2)
- Participant-specific plots of SAR441236 concentration throughout the study

5.10 Virology

- Primary efficacy outcome (Section 4.2.1)

- Secondary efficacy outcomes (Section 4.2.2)

5.11 Attributions of SAR441236 Antibodies (Section 4.2.2)

5.12 $CD4^+$ T-cell counts through study follow-up (Section 4.2.2)

6 Associated Documents

6.1 COVID-19 Appendix

On March 24, 2019 the A5377 team released a clarification memo to guide sites regarding how to handle study visits during the COVID-19 pandemic. In particular, this memo expanded the use of virtual visits and adjusted the visit schedule for participants in Cohort 4. New enrollments were paused.

Below is a description of the study status at the time of the COVID-19 pause and the accommodations made to the SAP. The timing of this pause resulted in the largest data collection impacts for Cohort 4 and Cohort 5. Primary and secondary PK outcomes will be affected and the secondary outcome regarding Week 12 CD4+ T-cell counts (#4).

General Considerations

The impact of COVID-19 on A5377 will be described in the report.

Arm A Single Dose Cohort (1-3) Considerations

- All follow-up for Cohort 1 and 2 participants was completed before the COVID-19 pause (i.e., all Cohort 1 and 2 participants were off study) and thus data collection was not affected.
- Before the COVID-19 pause, Cohort 3 was completely enrolled. Two participants had completed the specified 24-week follow-up and were off study. The remaining 4 participants had completed all visits *except* the final Week 24 visit. These visits were completed virtually during the COVID-19 pause and sites were instructed to have participants come in for a make-up in-person visit to collect Week 24 labs and be taken off study once site restrictions allowed research activities to resume.
- **IMPACT: LOW**
    - The Week 24 visit window will be expanded to capture the final in-person visit for these 4 participants.

Arm A Multi Dose Cohort (4) Considerations

- Nine participants had enrolled in Cohort 4 and received treatment before the COVID-19 pause (March 2020). Four participants had received 2 infusions before the pause while the remaining 5 participants had received a single infusion. All 9 participants missed 1 infusion (either the second or third) during the pause. Protocol Version 3.0 LOA #1 modified the dosing schedule to allow these participants to make-up their deferred infusion and resume scheduled visits.
- **IMPACT: MODERATE**
    - The primary PK endpoint has the potential to be affected, as the Week 12 visit was virtual for many participants. The A5377 team pharmacologist will make the appropriate accommodations in the calculation of the PK parameters and document them in the PK analysis plan.

- Analysis windows have been widened to capture as much information as possible. For participants who received their infusion shortly before the pause, they were directed to the Single Dose Arm A SOE (Table 6.1-1 in Protocol Version 2.0) after they had reached Week 4 to reduce site burden. This will cause slight differences in visit schedules across Cohort 4 participants. However, the majority of these were virtual (no lab data collected) so the need to align lab results (e.g., CD4+ T-cell counts) will be negligible.

Arm B Single Dose Cohort (5) Considerations

- Four participants were on-study in Cohort 5 during the COVID-19 pause. One participant had completed the specified 24-week follow-up and was off study before the pause. All participants had reached Day 28 and initiated ART by the end of February 2020.
- **IMPACT: MODERATE**
  - There is no impact to the primary efficacy outcome (i.e., all participants had reached Day 28 before the COVID-19 pause) nor to any secondary outcome involving HIV-1 RNA.
  - The primary PK endpoint has the potential to be affected as some Week 12 visits were conducted virtually (and thus no labs were collected). The A5377 team pharmacologist will make the appropriate accommodations in the calculation of the PK parameters and document them in the PK analysis plan.
  - Analysis windows have been widened to capture as much information as possible. The Week 24 visit window will be further expanded to capture in-person visits for all participants.
  - Note: Per Protocol Version 3.0 this Cohort 5 will be closed (although it did not enroll 6 participants).