Approvals

ACTG A5357

Primary Statistical Analysis Plan

Version 4.0

A Study of Long-Acting Cabotegravir Plus VRC-HIVMAB075-00-AB (VRC07-523LS) to Maintain Viral Suppression in Adults Living with HIV-1
Protocol v4.0

ClinicalTrials.gov Identifier: NCT03739996

August 22, 2023

This is the ACTG A5357 SAP Version 4.0 with names of authors, names of publication writing team members, and analysis timelines redacted.

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1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures of ACTG A5357 that will be included in the primary manuscript, and which address, at minimum, the major 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.

Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Statistical Analysis Report are included in the (separate) Analysis Implementation Plan (AIP). A separate Statistical Analysis Plan for other objectives and outcome measures will be developed once results for the Primary and Secondary Objectives are known, and analyses will be presented in a separate report.

Analyses for the Primary Analysis Report will begin once the last participant has completed the week **R2+**48 study visit, all adverse events (through Step 2) have been adjudicated by the core team, all queries have been resolved to the statistician's satisfaction in order to conduct the intended analyses. **A preliminary version of this report will be produced containing analysis of all outcomes observable once all participants have completed Step 2 and with preliminary looks at primary and secondary safety outcomes 10.2.1.1 and 10.2.2.11.**

The Primary Statistical Analysis Report will be used for submission of results to ClinicalTrials.gov. Results for primary outcomes are required to be submitted within one year of the primary completion date (PCD), which is the date the last participant is examined for the purposes of data collection for the latest observed primary outcome measure. For this study, the PCD is based on **101 weeks of follow-up** (5 weeks in Step 1, 48 weeks in Step 2 **and 48 weeks in Step 3**), **as adverse events observed on Step 3 are still being adjudicated with respect to CAB LA and VRC07-523LS.** A submission to ClinicalTrials.gov will be done once all follow-up (through Step 3) is complete.

1.2 Key SAP Updates

This is the initial version of the statistical analysis plan and there have yet to be any key updates. This section will be updated in future versions of the analysis plan.

Version	Changes Made	Effective Date
1.0	Original Version	13JAN2020
2.0	Letter of amendment review by [redacted] (LOA #1 and #2 for Protocol Version 3.0). Changes were minor and are bolded.	9/10/2020

2.1	Letter of amendment review by [redacted] (LOA #3 for Protocol Version 3.0). No changes were required.	7/21/2021
3.0	Protocol version 4.0 review by [redacted]. The word “oral” was removed when describing the SOC ART regimen participants begin in Step 3.	6/29/2022
4.0	Updates were made to capture extending the PCD to appropriately capture Step 3 adverse events which may contribute to outcome measures 10.2.1.1 and 10.2.2.11. **Major changes are bolded.**	August 22, 2023

2 Study Overview

2.1 Study design

Protocol Version 1.0 was finalized on October 2, 2018. Due to recommendations made by the FDA, the protocol was intended to open to enrollment under version 2.0 and not version 1.0. Protocol Version 2.0 was finalized on February 27, 2019. Due to new results in the field, VRC01LS was replaced by VRC07-523LS in protocol v3.0. The protocol will open to enrollment under version 3.0 and not version 2.0. Protocol Version 3.0 was finalized on October 18, 2019.

A5357 is a Phase II, single arm, open-label switch study to assess the safety, tolerability, pharmacokinetics, and antiviral activity of long-acting cabotegravir (CAB LA) plus the broadly neutralizing monoclonal antibody, VRC-HIVMAB075-00-AB (VRC07-523LS) in HIV-1-infected adults with suppressed plasma viremia.

At Step 1 entry, all participants will discontinue their current ART regimen except for nucleoside reverse transcriptase inhibitors (NRTIs), and initiate oral CAB (30 mg). Viral load monitoring will occur at entry and week 4 (and also at week 5 if HIV-1 RNA is 50-199 copies/mL at week 4). Participants tolerating oral CAB plus their current two NRTIs with HIV-1 RNA <50 copies/mL at week 4, or HIV-1 RNA of 50-199 copies/mL at week 4 followed by HIV-1 RNA <50 copies/mL at week 5, will register to Step 2 and receive CAB LA every 4 weeks through week R2+44 plus VRC07-523LS every 8 weeks through week **R2+40**. Participants in Step 1 who are not eligible for Step 2 entry will be switched to a standard of care (SOC) regimen and followed on study every 2 weeks for a total of 4 weeks and then be taken off study.

Viral load monitoring in Step 2 will occur every 2 weeks until week R2+8 and then every 4 weeks until week 48. All participants will complete the week R2+48 visit in Step 2, and this visit will be used to confirm virologic rebound in those with HIV-1 RNA ≥50 copies/mL at week R2+44.

For participants who have a confirmed HIV-1 RNA ≥200 copies/mL during Step 2 or confirmed HIV-1 RNA ≥50 copies/mL at week R2+44 and ≥200 copies/mL at week R2+48, genotypic testing will be performed

for protease/reverse transcriptase (PR/RT) and integrase resistance. In addition, samples from the failure confirmation visit and pre-ART or entry (if available) will be tested for viral clonality, integrase resistance, and VRC07-523LS neutralization resistance. These participants will be switched back to an SOC ART regimen, guided by resistance testing (Step 3).

All participants who receive any dose of CAB LA or VRC07-523LS or prematurely discontinue study treatment in Step 2 will register to Step 3 (the 48-week follow up on an SOC regimen) at the final study visit in Step 2 or at premature treatment discontinuation.

2.2 Hypotheses

The combination of long-acting cabotegravir (CAB LA) and VRC-HIVMAB075-00-AB (VRC07-523LS) is safe and will prevent viral rebound (confirmed HIV-1 RNA ≥200 copies/mL) in individuals who have achieved suppression with conventional antiretroviral therapy (ART).

2.3 Sample Size Considerations

Assuming 74 participants are enrolled, 70 initiate CAB LA plus VRC07-523LS, 10% are lost to follow-up and 5% subsequently discontinue CAB LA plus VRC07-523LS, there will be 60 analyzable participants. With 60 analyzable participants, if the observed virologic failure probability is 5.0%, the 95% CI will be [1.7%, 13.7%]. This 95% CI is estimated using the Wilson score method. A 95% CI of [1.7%, 13.7%] would provide proof of concept in support of the investigational strategy. Assuming the true rate of failure is 5%, the sample size will provide >90% power to reject a null failure rate of 20%. Regarding the assessment of safety and tolerability, a sample size of 70 CAB LA plus VRC07-523LS treated participants will provide a 94% probability of observing a CAB LA plus VRC07-523LS related AE or CAB LA plus VRC07-523LS related treatment discontinuation that would occur in 4% of treated participants.

Overall, the study aims to enroll at least 15 (20% of 74) female participants. The core team will also monitor accrual to ensure that ≥70 participants enroll in Step 2. Additional participants will be enrolled into the study if >4 Step 1 participants are ineligible for Step 2.

2.4 Study Monitoring

Accrual, baseline characteristics, study conduct (including premature treatment and study discontinuations), virologic failures, and all AEs will be monitored during the trial on a regular basis by the protocol core team. The protocol core team will review the individual safety data frequently to assess the relation of all reported AEs to oral CAB, CAB LA, and VRC07-523LS.

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.

To ensure the safety of the participants, the study will be reviewed routinely by an independent ACTG appointed study monitoring committee (SMC) at the earlier of (i) the 25th enrolled participant has reached week 24 in Step 2 of the CAB LA plus VRC07-523LS combination or discontinued the study or study

treatment prior to this, or (ii) 1 year after the study is open for enrollment. After the first interim review, the study will be routinely monitored annually by the SMC.

An interim review may be triggered prior to this if (i) three or more participants have virologic failures while adhering to Step 2 treatment (see below for definition of virologic failures considered in the stopping guideline), (ii) one or more participant(s) experience a death that is assessed by the protocol core team as possibly, probably, or definitely related to CAB LA and/or VRC07-523LS at any time, (iii) two or more participants experience a Grade 4 AE that is assessed by the protocol core team as possibly, probably, or definitely related to CAB LA and/or VRC07-523LS before 25 participants are enrolled and have reached week 24 of Step 2, or (iv) four or more participants experience a Grade 4 AE that is assessed by the protocol core team as possibly, probably, or definitely related to CAB LA and/or VRC07-523LS at any time. If an interim review is triggered, enrollment into Step 1 and Step 2 will be paused pending SMC consultation and participants in Step 1 or Step 2 will continue to follow the intended study design including continuing the step-specific study treatment regimen until the SMC has been consulted. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statisticians in consultation with the team.

To protect participants if virologic failure on the experimental regimen turns out to be higher than what may be clinically acceptable, a stringent stopping rule has been put into place. However, to guard against premature study stoppage or modification due to virologic failures that may be attributed to non-adherence or deviations from the specified dosing of the study treatments, virologic failures contributing to the stopping criteria must meet additional criteria to ensure that the pure treatment efficacy is evaluated. Specifically, virologic failure for the study's stopping guideline will be defined as two consecutive HIV-1 RNA levels ≥200 copies/mL on Step 2, while adhering to study treatment (i.e., no missed dose of CAB LA or VRC07-523LS). A missed dose is defined as an unadministered dose, inadequate dose, or any dose outside the window specified in the protocol. Initial HIV-1 RNA measurements ≥200 copies/mL taken prior to Step 2 treatment initiation will be excluded from the evaluation of virologic failure for the stopping guideline. Under this definition of virologic failure, a true failure rate ≤2% is considered to be acceptable. The reference for the threshold is the recent result from the LATTE-2 trial, where the virologic failure rate was 1% through week 96 for the combination of CAB LA plus RPV LA as a maintenance therapy for participants suppressed on ART.

Note that the virologic failure definition considered for the stopping guideline has more stringent adherence criteria than the virologic failure definition for the primary outcome, with the intention that the stopping guideline serves the purpose of protecting participants if available data indicate that efficacy of the experimental regimen may be lower than what is clinically acceptable. Table 10.5-1 (in the protocol) estimates the choices of the stopping guideline associated with different sample sizes and the probability that the guideline will be met under various true probabilities of failure. At any time during Step 2, if three or more participants are observed to experience virologic failures defined for the stopping guideline, enrollment into Step 1 and Step 2 will be paused, and SMC will be promptly convened. The SMC, in such an event, is expected to require all participants in Step 1 and Step 2 to enter Step 3 immediately. The stopping criteria will ensure that the trial has a high probability (≥85%) to continue when the true failure

rate is ≤2%, and is likely to stop when the true failure rate is unacceptably high (e.g., when the true failure rate is 10%, the trial will stop with a probability of 58%-95% when the sample size is ≥30).

The SMC safety triggers assume 95% of participants will initiate CAB LA plus VRC07-523LS, and have a low chance (9%) to be triggered if there is a low probability of a treatment related death (0.1%) and Grade 4 AE (1%), but a higher chance (97%) to be triggered if there is a high probability of a treatment related death (1%) and Grade 4 AE (10%).

2.5 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. Other study objectives in the protocol will be addressed in subsequent analysis plans.

2.5.1 Primary objectives:

- To evaluate the safety and tolerability of the combination of parenteral VRC07-523LS plus CAB LA in HIV-1 infected adults with well-controlled viral replication
- To evaluate the virologic efficacy of the combination of parenteral VRC07-523LS plus CAB LA to prevent viral rebound (confirmed HIV-1 RNA ≥200 copies/mL) in HIV-1 infected adults with well-controlled viral replication

2.5.2 Secondary Objectives:

- To determine the pharmacokinetic (PK) parameters of the combination of VRC07-523LS and CAB LA and their associations with viral rebound in HIV-1-infected adults
- To evaluate evidence of anti-idiotype antibodies against VRC07-523LS in samples collected from representative time points throughout the study
- To evaluate the safety and tolerability of oral CAB

2.6 Study Outcome Measures

This Primary SAP addresses the following primary and secondary outcome measures listed in the study protocol. Other study outcome measures in the protocol will be addressed in subsequent analysis plans.

2.6.1 Primary Outcome Measures

- Either the occurrence of a Grade 3 or higher AE that is possibly, probably, or definitely related (as judged by the core team) to the CAB LA plus VRC07-523LS combination or premature study treatment discontinuation due to an AE (regardless of grade) that is possibly, probably, or definitely related (as judged by the core team) to the CAB LA plus VRC07-523LS combination
- Virologic failure defined as confirmed HIV-1 RNA ≥200 copies/mL at or prior to week R2+44 of the CAB LA plus VRC07-523LS combination

2.6.2 Secondary Outcome Measures

2.6.2.1 PK parameters of the combination of VRC07-523LS and CAB LA

2.6.2.2 Viral resistance of breakthrough isolates

2.6.2.3 Virologic failure (confirmed HIV-1 RNA ≥200 copies/mL) at or prior to week R2+24 of the CAB LA plus VRC07-523LS combination

2.6.2.4 Virologic failure (confirmed HIV-1 RNA ≥200 copies/mL) or premature discontinuation of the CAB LA plus VRC07-523LS combination at or prior to week R2+44

2.6.2.5 Confirmed HIV-1 RNA ≥50 copies/mL at or prior to week R2+24 and R2+44 of the CAB LA plus VRC07-523LS combination

2.6.2.6 Confirmed HIV-1 RNA ≥50 copies/mL or premature discontinuation of the CAB LA plus VRC07-523LS combination at or prior to week R2+44

2.6.2.7 Virologic failure (defined by FDA snapshot algorithm) at week R2+44 of the CAB LA plus VRC07-523LS combination.

2.6.2.8 Measurable levels of anti-idiotype antibodies against VRC07-523LS in samples collected from representative time points throughout the study

2.6.2.9 Either the occurrence of a Grade 3 or higher AE that is possibly, probably, or definitely related (as judged by the core team) to oral CAB or premature oral CAB discontinuation due to an AE (regardless of grade) that is possibly, probably, or definitely related (as judged by the core team) to oral CAB

2.6.2.10 Premature discontinuation of oral CAB or the CAB LA plus VRC07-523LS combination

2.6.2.11 Occurrence of a Grade 3 or higher AE that is possibly, probably, or definitely related (as judged by the core team) to oral CAB or the CAB LA plus VRC07-523LS combination

3 Definitions

3.1 Baseline

"Study entry" or "baseline" is defined as the study registration date. The value used for baseline (Week 0) will be the last evaluation on or before the study registration date. **Although the protocol intended for the study/step entry visits to occur on the day of registration, this did not always occur. In these instances, the value used for baseline of "Step X Entry" will be the last evaluation on or before the study/step entry visit date. Note: Target dates for subsequent study visits are determined by step registration date, regardless of the date of the entry visit.**

Adverse events with an onset date on the study treatment initiation date and assessed by the site to have started before the administration of oral CAB, will be included as baseline.

3.2 Analysis populations

Participants found to be ineligible and who the study team determines should not be included in any analyses will be included in screening, accrual and eligibility summaries only.

Safety Analyses:

The primary safety analyses (10.2.1.1) will include all participants who have been exposed to CAB LA and VRC07-523LS**. All events observed on Step 2 and Step 3 (when the CMC assigned a relationship to Step 2 treatment) will be considered.**

The secondary safety outcomes (10.2.2.9, 10.2.2.10, and 10.2.2.11) will include all participants who have been exposed to oral CAB, as this population naturally encompasses all participants who were later exposed to CAB LA and VRC07-523LS.

Efficacy Analyses:

Primary and secondary virologic efficacy outcome (10.2.1.2, 10.2.2.3, 10.2.2.5) analyses will utilize the as-treated (i.e., per protocol) population, only including participant follow-up on the CAB LA plus VRC07-523LS combination. Participants who prematurely discontinue the CAB LA plus VRC07-523LS combination will be censored at the time of discontinuation.

Participants who have a single HIV-1 RNA ≥200 copies/mL at or prior week **R2+**44, who subsequently are lost to follow-up or discontinue study treatment, will be treated as virologic failure.

Analyses of the secondary virologic failure/premature treatment discontinuation outcomes (CAB LA plus VRC07-523LS) will include all participants initiating CAB LA plus VRC07-523LS.

4 Statistical methods

4.1 General considerations

Baseline characteristics will be summarized for the entire study population (i.e. participants that receive any dose of oral CAB, CAB LA or VRC07-523LS).

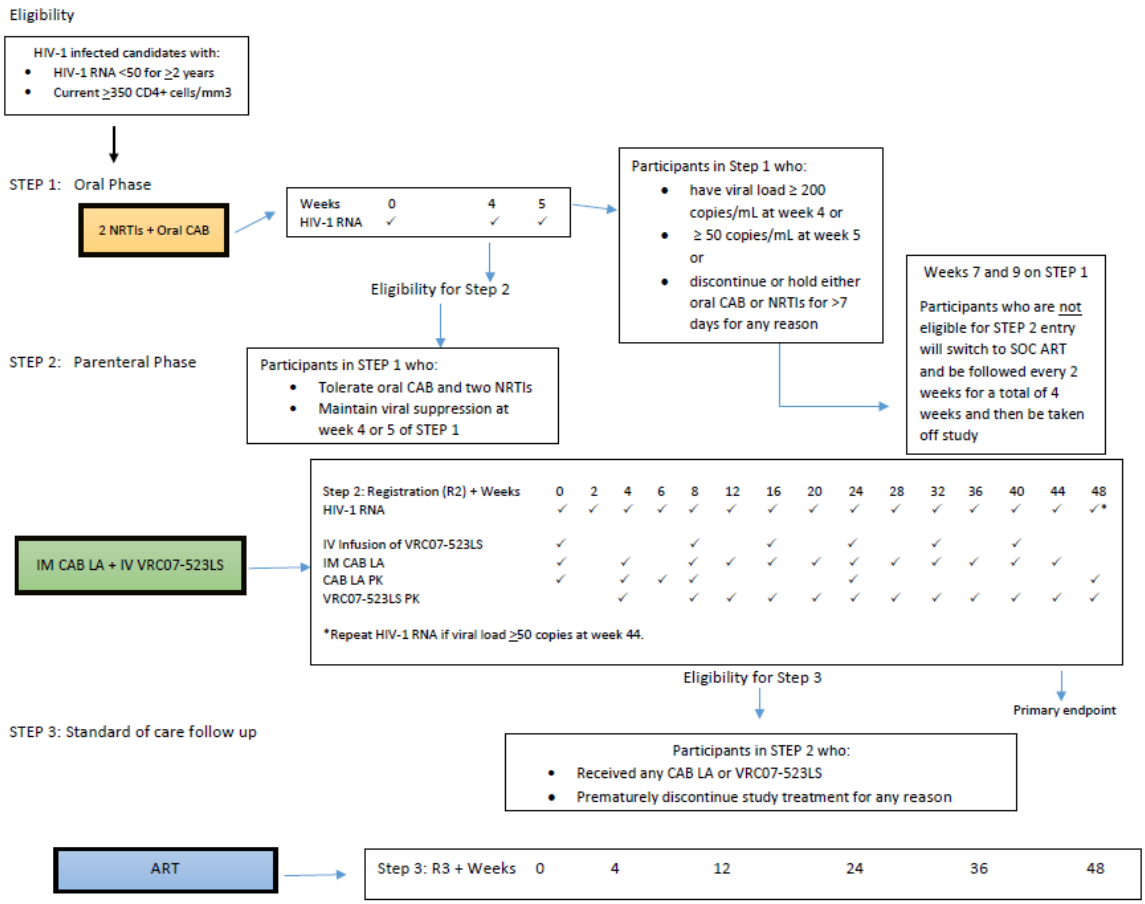
Statistical tests (all two-sided) will not be adjusted for interim monitoring. Significance levels where the p-value < 0.05 will be highlighted in the text, but must be interpreted with caution, since there will be multiple statistical tests which will increase the chance of spuriously significant p-values.

Categorical data will be summarized using N (%), and continuous data using N, min, Q1, median, Q3, max, and mean (standard deviation (SD)) (when appropriate). Any modifications to outcome measures after the team has seen data that were collected after entry will be identified as such in the analysis report.

4.2 Visit schedule and analysis windows

The study treatment administration and clinic visit schedules are summarized in Figure 1.

Figure 1: Study treatment administration and clinic visit schedules



For the purposes of analysis, visit windows will be formed around each study visit using the midpoints between adjacent weeks as cutoffs, and potentially including assessments collected outside the recommended visit windows described above. If there are multiple evaluations within the analysis window for a given visit, the evaluation closest to the scheduled study week will be used, and the earlier measurement will be used if there are two measurements which are equally distant from the scheduled week.

4.3 Primary Analyses

4.3.1 Primary Safety Analyses

Outcome measure: Either the occurrence of a Grade 3 or higher AE that is possibly, probably, or definitely related (as judged by the core team) to the CAB LA plus VRC07-523LS combination or premature study treatment discontinuation due to an AE (regardless of grade) that is possibly, probably, or definitely related (as judged by the core team) to the CAB LA plus VRC07-523LS combination

For the primary safety and tolerability analysis, all participants who have been exposed to CAB LA and VRC07-523LS will be included and summaries will include the number and percentage of participants experiencing a grade 3 or higher treatment-related AE or premature treatment discontinuation with a two-sided Wilson score 95% CI.

4.3.2 Primary Efficacy Analyses

Outcome measure: Virologic failure defined as confirmed HIV-1 RNA ≥200 copies/mL at or prior to week R2+44 of the CAB LA plus VRC07-523LS combination (where the starting time is the date of treatment initiation on Step 2).

For the primary virologic efficacy analysis, the cumulative probability of participants experiencing virologic failure at or prior to week R2+44 of the CAB LA plus VRC07-523LS combination will be estimated using Kaplan-Meier methods. If the probability is high, a standard two-sided 95% CI around the true virologic failure probability will be calculated using the adaption of Greenwood's variance estimate with a log(-log) transformation. However, if the probability is low, Rothman-Wilson two-sided 95% CIs will be estimated.

Primary virologic efficacy analysis will be as-treated (i.e. per protocol) only including participant follow-up on the CAB LA plus VRC07-523LS combination. Participants who prematurely discontinue the CAB LA plus VRC07-523LS combination will be censored at the time of discontinuation (as described in Section 3.2.)

4.4 Secondary Analyses

The secondary safety and tolerability outcome for the oral CAB (2.6.2.9) will be analyzed in a similar manner to the primary safety and tolerability outcome.

A similar approach will also be taken for the secondary safety outcome describing Grade 3 or higher AEs related to oral CAB or the CAB LA plus VRC07-523LS combination, overall and separately (2.6.2.11). In addition, all reported grade 3 or 4 AEs (regardless of study treatment relatedness) on oral CAB or the CAB LA plus VRC07-523LS combination will be summarized and tabulated.

Secondary intent-to-treat (ITT) sensitivity analyses will be conducted for the primary virologic efficacy outcome measure. Participants who initiate but then prematurely discontinue LA CAB plus VRC07-523LS will only be censored if lost to follow-up prior to virologic failure (defined as confirmed virologic failure or last available HIV-1 RNA ≥ 200 copies/mL). If not lost to follow up, HIV-1 RNA measures on Step 3 (SOC ART regimen) will be used to determine if the participant had virologic failure.

The secondary virologic efficacy outcomes will be analyzed in a similar manner to the primary efficacy outcome, but with respect to week **R2+**24 and/or ≥50 copies/mL (2.6.2.3, 2.6.2.5).

The secondary virologic failure/premature treatment discontinuation outcome will include all participants initiating CAB LA plus VRC07-523LS and consider both virologic failure and premature discontinuation of LA CAB plus VRC07-523LS as failure, whichever occurs first (2.6.2.4, 2.5.2.6).

The secondary premature treatment discontinuation outcome will include all participants initiating oral CAB and consider premature discontinuation of oral CAB, LA CAB or VRC07-523LS as failure, and will summarize them overall and separately with reasons for the discontinuation (2.6.2.10).

For the secondary analysis defining the virologic failure at week **R2+**44 endpoint using the FDA Snapshot Algorithm, see attachment #3 in the appendix for the derivation of virologic success and failure based on the decision tree algorithm. The FDA snapshot algorithm accounts for missing data by including a categorization of missed visits and study discontinuations; therefore, no special missing data methods will be used (2.6.2.7).

The percentage of participants with measurable levels of anti-idiotype antibodies will be presented along with a two-sided Wilson score 95% CI (2.6.2.8). Neutralization resistance and diversity of viral rebound quasispecies will be summarized pre-ART and at virologic failure (2.6.2.2).

For details on the determination of the PK parameters of the combination of VRC07-523LS and CAB LA, see the Pharmacology Plan in the protocol. Selected PK parameters will be summarized for all participants, and possibly by subgroup with viral rebound vs. maintaining viral suppression (2.6.2.1).

5 Report components

Detailed descriptions of the content of each of the following sections are provided in the Analysis Implementation Plan (AIP).

1. Study entry
    a. Screening
    b. Enrollment
    c. Eligibility errors
2. Baseline characteristics
3. VRC07-523LS susceptibility test results
4. Study status by Step
5. Study treatment status by Step
6. Changes/interruptions to study treatment during study follow-up by Step
7. Safety:
    a. Primary safety outcome
    b. Local injection and infusion site reactions
    c. Deaths
    d. Overall safety
8. Primary efficacy outcome (HIV-1 RNA)
    a. Evaluability
    b. Primary efficacy outcome
    c. Sensitivity analyses
    d. Secondary efficacy outcome
9. Virologic Failure and Viral Resistance

10. CD4 counts during study follow-up
11. HIV-1 RNA during study follow-up
12. CAB LA PK concentrations
13. VRC07-523LS PK concentrations
14. VRC07-523LS ADA