ACTG A5359

Primary Statistical Analysis Plan

Version 6.0

A Phase III Study to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals

Protocol Version: 4.0

ClinicalTrials.gov Identifier: NCT03635788

August 5, 2024

This is ACTG A5359 SAP Version 6.0 with names of authors, names of publication writing team members and analysis timeline redacted

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Version History

Version	Changes Made	Rationale	Effective Date
1	Original Version		Februry 13, 2019
1.1	LOA 1, 2, 3	➢ Reviewed LOA 1, 2, 3 ➢ New statistician is added on title page ➢ 'oral study-provided medications' is replaced by 'oral ART' throughout the document ➢ 2.3.2 objective 1.3.5: self-reported pill count is replaced by self-reported drug adherence ➢ 3.2: pill count outcomes are removed ➢ 'treatment' is replaced by 'treatment strategy' in 4.1.1 and 4.2.2 ➢ 4.2.1: one pf the sensitivity analysis is removed ➢ 4.2.2: pill count summaries are removed	April 22, 2020
2.0	LOA 4	➢ Reviewed LOA 4 ➢ Added definition of treatment discontinuation ➢ Rearrange the orders of outcome measures and report contents ➢ Updated FDA snapshot outcome measure to "≥50 copies/mL" for switch study ➢ Added COVID-19 appendix and primary estimand	December 8, 2022
3.0	Protocol v.2.0	➢ Change in study design includes Step 1 to Step 2 enrollment criteria, Step 2 virologic failure definition, sample sizes in Step 1 and Step 2, Steps 2 and 3 oral CAB/RVP lead-in option, etc. ➢ Replaced all language 'HIV-infected individuals' to 'persons with HIV' ➢ Updated some sensitive analyses to supportive analyses in primary and secondary analyses. ➢ Modification to analysis weeks due to COVID-19 ➢ Secondary outcome measure virologic failure updated to virologic non-success ➢ Added HIV-1 RNA <200 copies/mL in addition to all HIV RNA < 50 copies/mL summaries ➢ Added a statement saying additional supportive analyses may be conducted to explore the impact of COVID-19 with guidance from FDA, statistical, or clinical research	Novermber 10, 2021

		literature on approaches for analyzing clinical trial data impacted by COVID-19 ➢ Updated estimands using SDAC standard template, and added an estimand for a key secondary outcome measure.	
4.0	Protocol v.3.0	➢ Change in study design includes Step 1 to Step 2 enrollment criteria, wording in primary objective, outcome measure definitions to align with the intended analysis approach.	Februray 7, 2023
5.0	Protocol v3.0	➢ Added details on the approach for calculating information fraction at interim reviews ➢ The interim analysis will not take into consideration the impact of COVID disruption on participants, as the number of participants who were impacted is low. This factor will be considered in the final analysis.	July 20, 2023
6.0	Protocol v4.0	➢ Change in study design following DSMB recommendation from the Feburary 12, 2024 efficacy review ➢ Added subgroup analysis for age, BMI, Step 2 baseline RNA, CD4, and protocol version ➢ Changed evaluation of COVID impact to sensitivity analysis ➢ Added the definitions of delayed injections and missed injections ➢ Clarified treatment-related failure outcome measure ➢ Added BMI and fasting lipid change from Step 2 entry to week 48	August 5, 2024

1 Introduction

1.1 Purpose

This primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures of A5359 that will be included in the primary manuscript, which will address, at a 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, listings, 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.

Analyses outlined in this primary SAP will be performed once the last participant has completed study Step 2 (randomization phase) follow-up or after early termination of Step 2 based on Data Safety Monitoring Board's recommendation, all queries have been resolved, and the study data freeze has been completed and summarized in a primary analysis report. Results of the primary analysis will be published following the ACTG publication SOP.

A subset of these analyses will be provided in reports for the Data Safety Monitoring Board (DSMB) while the study is ongoing, which are limited to summaries that could lead to modification of the study. Reports provided to the DSMB are outlined in the Study Progress, Data, and Safety Monitoring Plan (SPDSMP).

Outlines of analyses for other objectives and outcome measures not included in the primary SAP will be provided in separate analysis plans for Other Objectives. Those analyses will be performed upon completion of the study.

This analysis plan may be modified by the study team as new information becomes available or to reflect recommendations of the DSMB. In addition, some analyses may be omitted if there is insufficient information.

1.2 Version History

Major revisions in v.2.0 included update the Plan to LOA 1-4 (e.g., adding COVID-19 appendix, removing objective and outcome measure related to pill count). Other revisions included SDAC Standard Operating Procedures governing IMPAACT and ACTG clinical trial SAPs (CLIN.10070 Statistical Analysis Plan (SAP) Version 8.3), and rearranging outcome measures to align with objectives.

Major revisions in v.3.0 included updates in Protocol v.2.0 (e.g. Step 1 to Step 2 enrollment criteria, Step 2 virologic failure definition, new sample sizes in Step 1 and Step 2, Steps 2 and 3 oral CAB/RVP lead-in option, etc.), added COVID-19 notes for the primary and secondary analyses, and modification to analysis weeks due to COVID-19. Other revisions included updating the primary estimand using SDAC's template and adding a new estimand for a key secondary objective.

Major revisions in v.4.0 included updates in Protocol v.3.0 (e.g., Step 1 to Step 2 enrollment criteria, wording change in primary objective, and updates to outcome measures from "time to" type of outcome to "occurrence" type of outcome to align with the intended analysis approach.)

Major revisions in v.5.0 included details on the approach used to calculate the information fraction for interim reviews and the change of plan to evaluate the impact of COVID disruption for interim analyses.

Major revisions in v.6.0 included changes in study design following DSMB recommendations from the Feburary 12, 2024 interim efficacy review. Other changes include adding subgroup analysis for age, BMI, Step 2 baseline RNA, CD4 count, and protocol version, changing evaluation of COVID impact to sensitivity analysis, adding the definition of delayed injections and missed injections, clarified treatment-related failure outcome measure and adding evaluation of BMI and fasting lipid changes from Step 2 entry to week 48.

2 Study Overview

At the 4th interim efficacy review on February 12, 2024, DSMB recommended stopping randomization to Step 2 and transitioning all eligible participants in Steps 1 and 2 to Step 3. Step 3 and Step 4 of the study continue as planned.

Study screening and enrollment to Step 2 were closed on February 16, 2024. Study enrollment was closed on April 16, 2024. Protocol v.4.0 implemented DSMB recommendations and removed Step 2. Participants in Step 1 who achieve virologic suppression (HIV-1 RNA ≤ 200 copies/mL) at or after Step 1, week 4, will register directly to Step 3 and receive LA ART. Participants in Step 2 will register to Step 3 if they are eligible. No changes are made to Step 3 and Step 4 follow-up.

The sections below summarize the study design for Protocol v.3.0.

2.1 Study Design

A5359 is a phase III, prospective, randomized, open-label trial comparing Long-Acting (LA) Antiretroviral therapy (ART) with rilpivirine (RPV) LA and cabotegravir (CAB) LA versus Standard of Care (SOC) in previously non-adherent individuals. The study has four Steps:

Step 1: Participants will be initiated on a SOC oral induction regimen consisting of a ≥3 drug ART regimen with ≥2 drugs predicted to be fully active including a boosted protease inhibitor (PI/cobi) and/or an integrase strand transfer inhibitor (INSTI) for up to 24 weeks. Participants who achieve milestones will receive conditional economic incentives (CEI) at Step 1.

Step 2: Step 1 participants are eligible to enter Step 2 if virologic suppression criteria for randomization are met at or after Step 1, week 4 (but before Step 1, week 24). Virologic suppression criteria are defined as: a) HIV-1 RNA ≤200 copies/mL or b) HIV-1 RNA of 201-399 copies/mL followed by HIV-1 RNA ≤200 copies/mL prior to Step 1, week 24. Eligible participants will enter Step 2 and be randomized 1:1 to switch to oral RPV + oral CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA every 4 weeks (Q4) until the end of Step 2 or to continue on SOC for 52 weeks. Randomization will be carried out using permuted blocks across sites with dynamic balance within site.

Step 3: At the completion of Step 2, eligible participants randomized to SOC will have the option to register to Step 3 and cross over to the LA strategy, which includes oral RPV+CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA Q4 weeks until the end of Step 3; participants already on RPV-LA + CAB-LA in Step 2 will continue on this regimen in Step 3 for 52 weeks.

Step 4: At the completion of Step 3, participants will transition to locally sourced commercial RPV LA + CAB LA, if possible and available. If access to locally sources commercial RPV LA + CAB LA cannot be obtained or participant requests to switch to oral ART, those participants will enter Step 4 and be followed for 52 weeks on locally sourced oral ART. If the participant can access to LA ART during follow-up in Step 4, and the participant and provider decide to restart LA ART, they will be allowed to do so. In that case, the participants will no longer need to be seen by the study after restarting LA ART.

In addition, any participant who receives at least one dose of CAB-LA or RPV-LA, and prematurely discontinues study treatment prior to end of Step 3, will be followed on locally sourced oral ART for 52 weeks after thier last dose of any LA injectable.

2.1.1 Duration

Up to 180 weeks (up to 24 weeks in Step 1, 52 weeks in Step 2, 52 weeks in Step 3, and up to 52 weeks in Step 4).

2.1.2 Sample Size

A maximum of 640 participants in Step 1 for Step 2 to achieve an accrual target of 320 participants (160 in each arm).

2.1.3 Study Population

Eligible participants are ART-experienced, non-pregnant people with HIV-1 who are ≥ 18 years of age with:

- Evidence of prior history of non-adherence
- No evidence of any clinically relevant RPV or INSTI resistance-associated mutations through commercially available resistance testing analyses (historically or upon screening).
- Ability of site clinician, in conjunction with participant, to construct a ≥3 drug ART regimen with ≥2 drugs predicted to be fully active, including a boosted PI/cobi and/or an INSTI. Drugs for oral regimens will be made available to study participants according to PSWP.

2.1.4 Regimen

Step 1 (Induction): All participants will receive the SOC (oral induction ART regimen) with CEI for up to 24 weeks.

Step 2 (Randomization): Participants who achieve virologic suppression criteria at or after Step 1, week 4 will be randomized at Step 2 in a 1:1 ratio to either of the two treatment arms:

- Arm A: Oral RPV + oral CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA Q4 weeks until the end of Step 2.
- Arm B: Continuation of SOC for 52 weeks.

Step 3 (Continuation/Crossover):

- Arm A participants (LA ART arm) will continue on RPV-LA + CAB-LA Q4 weeks for 52 weeks until completion of Step 3.
- Arm B participants (SOC arm) who are virologically suppressed (HIV-1 RNA ≤200 copies/mL) at Step 2, week 48, or HIV-1 RNA of 201-399 copies/mL at Step 2, week 48 followed by HIV-1 RNA ≤200 copies/ML by Step 2, week 52, will have the option to switch to oral RPV + oral CAB for 4 weeks (optional) followed by RPV-LA + CAB-LA Q4 weeks until the end of Step 3.

Step 4 (Observation): All participants who enter Step 4, as outlined in study design above, will be followed until they complete 52 weeks on locally sourced oral ART or restart LA ART if it becomes available.

2.1.5 Randomization

There is no randomization in Step 1. In Step 2, eligible participants will be randomized 1:1 to each of the two arms of the study. Randomization will be carried out using permuted blocks across sites with dynamic balance within site via a computer algorithm at the DMC. There is no randomization in Step 3 and Step 4.

2.2 Hypothesis

After achieving suppression during a period of incentivized SOC (up to 24 weeks), LA ART consisting of RPV-LA + CAB-LA will be a more successful therapy compared to a SOC regimen in keeping previously non-adherent persons with HIV on treatment and virologically suppressed.

2.3 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. Analysis of the primary and secondary efficacy objectives below will be analyzed under a superiority testing framework.

2.3.1 Primary Objective

- Objective 1.2: To compare regimen efficay of LA ART (using RPV-LA and CAB-LA) to SOC in previously non-adherent persons with HIV by 48 weeks of follow-up after an incentivized oral induction period

2.3.2 Secondary Objectives

- Objective 1.3.1: To compare virologic efficacy between LA ART using RPV-LA and CAB-LA and SOC at 48 weeks following an incentivized oral induction period in previously non-adherent persons with HIV.

- Objective 1.3.2: To assess the safety and tolerability of the LA ART regimen versus the SOC regimen in previously non-adherent persons with HIV after an incentivized oral induction period.

- Objective 1.3.3: To estimate the HIV-1 RNA viral decline at 4, 8, 12, 16 and 20 weeks after initiation of oral ART in Step 1 in previously non-adherent persons with HIV utilizing CEI to promote adherence.

- Objective 1.3.4: To assess participant acceptability and treatment satisfaction with LA ART versus SOC.

- Objective 1.3.5: To compare adherence [self-reported, drug adherence for SOC arm, self-efficacy, and missed or delayed injections (defined as 8 days beyond scheduled injection day) for LA ART], among previously non-adherent persons with HIV randomized to LA ART versus SOC.

- Objective 1.3.6: To compare the rates of new drug-resistance mutation development in individuals who develop virologic failure between the LA ART versus SOC and determine factors associated with emerging drug resistance.

2.4 Overview of Sample Size Considerations

A maximum of 640 participants need to be enrolled in Step 1, for Step 2 to achieve an accrual target of 320 participants (160 in each arm). Screening and enrollment into Step 1 will stop when 320 participants have enrolled into Step 2. The sample size estimation is based on the following considerations:

- The study should have approximately 80% power to show superiority of the LA ART compared to daily SOC with respect to the Step 2, week 48, cumulative probability of regimen failure.
- The study should have at least 80% power to show superiority of the LA ART compared to daily SOC with respect to the Step 2, week 48, cumulative probability of virologic failure.
- The cumulative probability of virologic failure by Step 2, week 48, is estimated to be 25% for the SOC arm and 9% for the LA ART strategy.
- The cumulative probability of regimen failure by Step 2, week 48, is estimated to be 50% for the SOC arm and 34% for the LA ART strategy assuming 5% treatment-related failures other than virologic in both arms.
- Given the targeted study population of previously non-adherent people with HIV-1, it is further assumed that 50% of participants who enroll in Step 1 will be lost to follow-up and/or ineligible to enter Step 2.
- The lost to follow-up rate (non-treatment related) will be constant during the study follow-up with a Step 2, week 48, cumulative lost to follow-up rate of 25% for each arm taking into consideration of possible impact of COVID-19 pandemic on clinical research activities.
- Sample size inflation of 2% is allowed to account for interim monitoring.

Please refer to the study protocol for additional details.

2.5 Overview of Formal Interim Monitoring

The study will be reviewed by the DAIDS Therapeutics and Prevention Data Safety Monitoring Board (TPDSMB). The first review will occur approximately 6 months after the accrual of the first participant. Subsequent reviews will take place at approximately yearly intervals after the first review, or per request by the DSMB. These reviews will assess study conduct and safety.

Two interim efficacy reviews are planned when approximately 33% (n=105) and 67% (n=214) of the targeted sample size for Step 2 (n=320) has completed Step 2 or experienced the primary outcome measure. Interim efficacy analyses will be based on group-sequential repeated confidence intervals for the difference between treatment groups, using the Lan-DeMets approach with an O'Brien-Fleming spending function. If the confidence interval excludes zero, demonstrating that one arm is superior to the other, or if external results convincingly establish the superiority of one arm over the other, then consideration should be given to recommending modification of the study. Interpretation and the consistency of the primary analysis with the results for secondary efficacy outcome measures and safety should be considered by the DSMB prior to recommending stopping a study arm.

The information fraction will be based on primary outcome measure and estimated using the effective sample size approached outlined in Tsiatis and Davidian (Statistics in Medicine, 2022). For simplicity, the same nominal type I error will used for the key secondary outcome measures although the level of information available at the time for the secondary outcomes may be different from the primary outcome measure.

The data for COVID -19 disrutpion at sites were presented in the March 2023 DSMB. A total of 6 sites were disrupted due to COVID-19. The disruption duration ranges from 20 weeks to 42 weeks. One site closed for clinical study related events, 2 sites stayed open, unable to provide oral lead-in or oral ART, but continued to have on-site visits and injections for participants on LA ART, and 3 sites stayed open but were unable to provide LA-ART or oral ART. A total of 10 participants were on Step 2 at these sites during the period of disruption. Since the number of participants who were impacted by the COVID disruption at sites is low, the interim analysis will not take this factor into consideration for related outcome measures. This will be included in the final analysis.

Please refer to the study protocol for additional details.

3 Outcome Measures

The following are the primary and secondary outcome measures listed in protocol section 10.2.

An endpoint adjudication committee consisting of one or more independent clinicians will review regimen failures (including virologic failure and study treatment discontinuation, as defined below).

3.1 Primary Outcome Measure

- Occurrence of regimen failure in Step 2 [Outcome 10.2.1]

The primary outcome measure to be used to address the study's primary objective [Objective 1.2] is the occurrence of regimen failure in Step 2.

NOTE A: Regimen failure is defined as the occurrence of the first of the following two events at any time post randomization and Step 2, week 48 visit:

- Virologic failure
- Permanent discontinuation of randomized study treatment

  See section 3.2 for virologic failure definition and analysis details.

NOTE B: Permanent discontinuation of randomized study treatment is defined as the first of the following events:

- Participants randomized to LA ART arm prematurely discontinue oral RPV or CAB before Step 2, week 4.
- Participants randomized to LA ART arm never initiate injectable RPV or CAB.
- Participants randomized to LA ART arm prematurely discontinue injectable RPV or CAB.
- Participants randomized to SOC arm prematurely discontinue oral ART regimen. Switching to another oral ARV is not considered treatment discontinuation.
- Participants prematurely discontinue study treatment/participation for any reason including death and loss to follow up.

NOTE C: Participants who did not experience a regimen failure on Step 2 will be censored at Step 2 week 48 visit or Feburary 12, 2024, whichever is earlier.

NOTE D: The time of virologic failure will be the week associated with the first of the 2 consecutive samples meeting the virologic failure definition. The time to permanent treatment discontinuation will be the week in which the permanent discontinuation occurred.

NOTE E: Eligible participants who never started treatment after randomization will be considered as having a regimen failure at the randomization date.

NOTE F: Per protocol section 9.2, a criterion for premature study discontinuation is failure by the participant to attend 3 consecutive study visits. If a participant misses 3 consecutive study visits, then the participant will be considered as having a regimen failure at the earliest of the first of the 3 missed visits and the treatment discontinuation date.

NOTE G: If a participant has not met the criterion for premature study discontinuation (i.e. misses 3 consecutive study visits) but the participant has missed their week 48 and week 52 visits, then the participant will be considered as having a regimen failure at the earliest of week 48 and the treatment discontinuation date. If a participant is seen and evaluated post week 52, then the team will decide if the participant's evaluations will be counted as part of the week 52 visit.

3.2 Secondary Outcome Measures

Outcomes Associated with Secondary Efficacy Objectives (Objectives 1.3.1 and 1.3.3)

1. Occurrence of virologic failure in Step 2 at any time post randomization and week 48 visit [Outcome 10.2.2.1]

   Virologic failure confirmation will be determined based on any two consecutive evaluations meeting the virologic failure criterion (HIV-1 RNA > 200 copies/mL after Step 2 randomization) regardless of the time between them.

   Only HIV-1 RNA measurements obtained prior to or on February 12, 2024 would be considered as initial failing measurements. Confirmatory measurements may be obtained prior to or on March 4, 2024 (within 21 days after February 12, 2024). If no confirmatory measurements are available within the time frame (prior to or on March 4, 2024), participants with an initial failing HIV-1 RNA measurement prior to or on February 12, 2024 will be considered as virologic failure at the study visit week of the unconfirmed value.

   Participants discontinuing the study/Step 2 (for any reason, including death and end of study Step) will be handled as follows:

   - Participants with an unconfirmed virologic failure (last Step 2 HIV-1 RNA >200 copies/mL after Step 2 randomization) will be considered as virologic failure at the study visit week of the unconfirmed result.
   - All remaining participants without experiencing VF will have their follow-up time censored at the study week of their last measured plasma HIV-1 RNA sample on Step 2 or February 12, 2024, whichever is earlier.

   Note: Participant with no HIV-1 RNA on Step 2 will be censored at randomization.

2. Occurrence of treatment-related failure in Step 2 at any time post randomization and week 48 visit [Outcome 10.2.2.2]

   Treatment-related failure is defined as the first of the following events:

   - Virologic failure (as defined above)
   - Treatment discontinuation due to AE

   Note: Only treatment discontinuation due to AE (or death) that are considered related to treatment (determined by site investigators) will be used to determine the outcome measure.

For participants who do not experience treatment-related failure, their follow-up time will be censored at their last study visit (any type) week on Step 2 up to week 48 visit or February 12, 2024, whichever is earlier.

3. Virologic non-success defined by FDA Snapshot algorithm at Step 2, week 48 [Outcome 10.2.2.3]

4. Plasma HIV-1 RNA level < 50 copies/mL and ≤ 200 copies/mL at scheduled study visits on Step 1 and 2 [Outcome 10.2.2.4]

Outcome Associated with Secondary Drug-Resistance Objective (Objective 1.3.6)

5. New drug-resistance mutation in participants with virologic failure in Step 2 [Outcome 10.2.2.10]

Outcomes Associated with Secondary Safety and Tolerability Objective (Objective 1.3.2)

6. Occurrence of adverse event (as defined in protocol section 7.2) during Step 1 and 2 [Outcome 10.2.2.5]

7. Occurrence of discontinuation of randomized treatment in Step 2 at any time post randomization up to week 48 visit [Outcome 10.2.2.6]

   Treatment discontinuation is defined in **Section 3.1**, NOTE B.

   NOTE A: Participants who did not discontinue randomized study treatment will be censored at Step 2 week 48 visit or February 12, 2024, whichever is earlier.

   NOTE B: Eligible participants who never started treatment after randomization will be considered as having a discontinuation of treatment at the randomization date.

   NOTE C: Per protocol section 9.2, a criterion for premature study discontinuation is failure by the participant to attend 3 consecutive study visits. If a participant misses 3 consecutive study visits, then the participant will be considered as having treatment discontinuation at the earliest of the first of the 3 missed visits and the treatment discontinuation date.

   NOTE D: If a participant has not met the criterion for premature study discontinuation (i.e. misses 3 consecutive study visits) but the participant has missed their week 48 and week 52 visits, then the participant will be considered as having treatment discontinuation at the earliest of week 48 and the treatment discontinuation date. If a participant is seen and evaluated post week 52, then the team will decide if the participant's evaluations will be counted as part of the week 52 visit.

8. Occurrence of Injection Site Reactions (ISR) during Step 2 [Outcome 10.2.2.11]

Outcomes Associated with Secondary Treatment Satisfaction/Acceptability Objective (Objective 1.3.4)

9. Summary score of HIV Treatment Satisfaction Questionnaire (HIVTSQ) in Step 2 [Outcome 10.2.2.7]

Outcomes Associated with Secondary Adherence Objective (Objective 1.3.5)

10. Occurrence of missed or delayed (defined as 8 days beyond scheduled injection day) injections for participants who received LA ART in Step 2 [Outcome 10.2.2.8]

11. Summary scores of HIV Treatment Adherence Self-Efficacy Scale in Step 1 and Step 2 [Outcome 10.2.2.9]

12. Summary of Self-report dichotomous preference questionnaire [Outcome 10.2.2.12]

4 Estimands

An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarizes at a population level what the outcomes would be in the same participants under different treatment conditions being compared. The description of an estimand involves precise specifications of certain attributes, which should be developed based not only on clinical considerations but also on how intercurrent events are reflected in the clinical question of interest. See ICH E9 (R1) addendum on Estimands and Sensitivity Analysis in Clinical Trials.

4.1 Estimand for primary objective

Primary Objective: To compare regimen efficacy of LA ART (using RPV-LA and CAB-LA) to SOC in previously non-adherent persons with HIV by 48 weeks of follow-up after an incentivized oral induction period.	
Estimand description	Absolute difference in the cumulative probability of regimen failure over 48 weeks of LA ART (using RPV-LA and CAB-LA) compared to SOC, among previously non-adherent, HIV-infected individuals who successfully achieve virologic suppression after a period of incentivized SOC ART regimen
Treatment	LA ART (using RPV-LA and CAB-LA) vs. SOC (oral ART)

Target population	**Analysis set**
Previously non-adherent, ART experienced individuals living with HIV who successfully achieved virologic suppression after a period of incentivized SOC oral ART regimen	Participants who are randomized in Step 2
Variable(s)	**Outcome measure(s)**
Occurrence of regimen failure	Occurrence of regimen failure in Step 2 (from Step 2 randomization to up to week 48 visit)
Handling of intercurrent events	**Handling of missing data**
1. Failure to start LA ART treatment strategy after randomization or discontinue assigned oral ART on or before the date of randomization: included as part of the outcome measure definition as failure events (composite strategy) 2. Permanent discontinuation of study treatment or study participation: included as part of the outcome measure definition as failure events (composite strategy) 3. Death/loss to follow-up – included as part of the outcome measure definition as failure events (composite strategy) 4. Missed Injection (unless bridged with oral CAB + RPV or oral ART): ignored (treatment policy strategy) 5. COVID disruption defined by site: ignored (treatment policy strategy)	For the primary analysis, a censoring-at-random (CAR) assumption. Analysis model is Kaplan-Meier estimation, compatible with CAR.
Population-level summary measure	**Analysis approach**
Absolute difference between LA ART and SOC in cumulative probability of regimen failure over 48 weeks	Comparison of treatment arms will be made using the difference in the Kaplan-Meier estimate for the week 48 cumulative probability of regimen failure. Specifically, Kaplan-Meier estimates of the 48-week cumulative probabilities of regimen failure and associated Greenwood variance will be calculated.

Sensitivity analysis for assesing impact of COVID-19 disruption:

4.1.1 Censoring at Site Level:

Intercurrent events:

1. Failure to start LA ART treatment strategy after randomization or discontinue assigned oral ART on or before the date of randomization: included as part of the outcome measure definition as failure events (composite strategy)
2. Permanent discontinuation of study treatment or study participation: included as part of the outcome measure definition as failure events (composite strategy)
3. Death/loss to follow-up: included as part of the outcome measure definition as failure events (composite strategy)
4. Missed Injection (any dose, unless bridged with oral CAB + RPV or oral ART): will be ignored (treatment policy strategy)
5. COVID disruption defined by site: at sites where COVID disruption period is defined, participants' follow-up will be censored at the start date of COVID disruption (while-on-treatment strategy)

Population-level summary: Absolute difference between LA ART and SOC in cumulative probability of regimen failure over 48 weeks

Notes on missing data:
For this analysis, a censoring-at-random (CAR) assumption. Analysis model is Kaplan-Meier estimation, compatible with CAR.

4.2 Estimand for Key Secondary Objective

<table>
<tr><td colspan="2">Secondary Objective: To compare virologic efficacy between LA ART using RPV-LA and CAB-LA and SOC at 48 weeks following an incentivized oral induction period in previously non-adherent persons with HIV</td></tr>
<tr><td>Estimand description</td><td>Absolute difference in the cumulative probability of virologic failure over 48 weeks of LA ART (using RPV-LA and CAB-LA) compared to SOC, among previously non-adherent, HIV-infected individuals who successfully achieve virologic suppression after a period of incentivized SOC ART regimen.</td></tr>
<tr><td>Treatment</td><td>LA ART (using RPV-LA and CAB-LA) vs. SOC (oral ART)</td></tr>
<tr><td>Target population</td><td>Analysis set</td></tr>
<tr><td>Previously non-adherent, ART experienced individuals living with HIV who successfully achieved virologic suppression after a period of incentivized SOC oral ART regimen</td><td>Participants who are randomized in Step 2</td></tr>
<tr><td>Variable(s)</td><td>Outcome measure(s)</td></tr>
<tr><td>Occurrence of virologic failure</td><td>Occurrence of virologic failure in Step 2 (from Step 2 randomization to up to week 48 visit)</td></tr>
<tr><td>Handling of intercurrent events</td><td>Handling of missing data</td></tr>
<tr><td>1. Failure to start LA ART treatment strategy after randomization or discontinue assigned oral ART on or before the date of randomization: ignored (treatment policy strategy)
2. Permanent discontinuation of study treatment: Ignored (treatment policy strategy)
3. Permanent discontinuation of study participation: censored (hypothetical strategy)
4. Death/loss to follow-up: censored (hypothetical strategy)
5. Missed Injection (unless bridged with oral CAB + RPV or oral ART): ignored (treatment policy strategy)
6. COVID disruption defined by site: ignored (treatment policy strategy)</td><td>For the primary analysis, a censoring-at-random (CAR) assumption. Analysis model is Kaplan-Meier estimation, compatible with CAR.</td></tr>
<tr><td>Population-level summary measure</td><td>Analysis approach</td></tr>
<tr><td>Absolute difference between LA ART and SOC in cumulative probability of virologic failure over 48 weeks</td><td>Comparison of treatment arms will be made using the difference in the Kaplan-Meier estimate for the week 48 cumulative probability of virologic failure. Specifically, Kaplan-Meier estimates of the 48-week cumulative probabilities of regimen failure and associated Greenwood variance will be calculated.</td></tr>
</table>

5 Statistical Principles

5.1 General Considerations

5.1.1 Analysis Populations

Intention-to-Treat (ITT) population is defined as all participants who were randomized to the treatment arms, regardless of status on randomized treatment. Participants will be assessed according to their randomized treatment, regardless of the treatment they received. The population used in the primary efficacy analyses will be the ITT population. For analyses involving outcomes in Step 1, the ITT population will be defined as all participants who registered to Step 1, regardless of status on treatment.

Modified Intention-to-Treat (mITT) population is defined as all participants who were randomized to the treatment arms and received at least one dose of study treatment at or after randomization. Participants will be assessed according to their randomized treatment.

- For analyses involving outcomes in Step 1, the mITT population will be defined as all participants who registered to Step 1 and received at least one dose of study treatment within 28 days of study initiation.
- For analyses involving outcomes in Step 2, the mITT population will be defined as all participants randomized to Step 2 and received at least one dose of study treatment, regardless of when treatment was initiated.

As-treated population is defined as all participants on randomized treatment. Participants will be assessed according to actual treatment strategy received. For analyses involving outcomes in Step 1, the as-treated population will be defined as all participants who registered to Step 1 and on treatment. See **Section 5.3** for details regarding how participants will be censored in the Step 2 analyses for each particular outcome.

For all analysis populations, participants who were registered/randomized and later found to be ineligible for A5359 by the site, study statistician(s), or data manager will be reviewed by the study co-chairs and co-vice chairs for confirmation of their ineligibility and whether to be included in the analyses.

5.1.2 Definitions and Use of Visit Windows for Analysis

Step 1 (Induction)

Clinic visits in Step 1 take place at screening, study entry (which may be the same day as screening), and Step 1 weeks 2, 4, 8, 12, 16, 20, and 24. Step 1 participants are eligible to enter Step 2 if virologic suppression criteria for randomization are met at or after Step 1, week 4 (but before Step 1, week 24). Virologic suppression criteria are defined as: a) HIV-1 RNA ≤200 copies/mL or b) HIV-1 RNA of 201-399 copies/mL followed by HIV-1 RNA ≤200 copies/mL prior to Step 1, week 24. Note that Step 1, week 24 evaluations will only be performed for participants who are not eligible before week 24 or choose not to continue onto Step 2. Scheduled visit windows for all visits after entry are ± 1 week.

Analysis windows will be defined in details in AIP. See additional note regarding COVID disruption (**Section** Error! Reference source not found.).

Step 2 (Randomization)

Step 2 randomization is defined as 3 to 5 weeks after the participant's visit used to determine HIV-1 RNA suppression criteria has been completed. For participants randomized to LA ART, clinic visits in Step 2 take place at Step 2 randomization and every 4 weeks after randomization until Step 2, week 52. For participants randomized to SOC, clinic visits in Step 2 take place at Step 2, randomization and Step 2, weeks 4, 8, 16, 24, 36, 48, and 52.

For participants randomized to LA ART, scheduled visit windows for Step 2, week 4a* is +1 week for OLI and ±4 days for non-OLI; Step 2, week 4b* is +6 days (note: participants who are randomized to LA ART in Step 2 and who are opting to start OLI must have results from the Week 4a* clinical and laboratory evaluations resulted and reviewed by the IoR or their designee prior to the injections in week 4b*); and for Step 2, weeks 8 is ±4 days, week 12 is ±4 days for OLI and ±1 week for non-OLI. Scheduled visit windows for all visits after Step 2, week 12 are ± 1 week. For participants randomized to SOC, scheduled visit windows for all visits after Step 2 randomization are ± 1 week.
(* refer week 4a and week 4b to protocol section 6.)

If there are multiple evaluations within the window for a given visit, the evaluation closest to the scheduled visit week will be used in analyses.

Analysis window will be defined in detail in AIP. See additional note regarding COVID disruption (**Section** Error! Reference source not found.).

5.2 Discontinuation of Study Treatment

Step 1 (Induction)

Discontinuation of study treatment during Step 1 oral induction is permenant discontinuation of oral ART regime. Modification to oral ART regimen including switching or discontinuing one ARV drug is not considered permenant discontinuation. The date of discontinuation is the day after the last dose date reported.

Step 2 (Randomization)

Discontinuation of study treatment for oral SOC arm is permenant discontinuation of oral ART regimen. Modification to oral ART regimen including switching to other oral ART regimen, switching from study provided oral ARV regimen to locally sourced oral ARV regimen, or discontinuing one ARV drug is not considered permenant discontinuation. The date of discontinuation is the day after the last dose date reported.

Discontinuation of study treatment for LA ART arm is permenant discontinuation of oral CAB or oral RPV before Step 2 week 4 and not initiated LA injectables for those chose OLI, never initiated LA injectables, or discontinued RPV or CAB injectables by visit week 48. For those who permenantly discontinued oral CAB/RPV or completed oral CAB/RPV and never initiated LA injectables, the date of disconintuation is the day after the last dose of oral CAB/RPV. For those who permenantly discontinued LA injectiables, the date of discontinuation is the date of the next scheduled injection (4 weeks from the last injection) (Kroken, 2014). For those who never initiated study treatment, the date of discontinuation is the date of randomization.

5.3 Data cutoff date

Following the DSMB recommendation on February 12, 2024, outcome measures (in section 3.0) associated with study visits up to or on February 12, 2024 will be included in the primary analysis. The one exception is the confirmatory HIV-1 RNA measurements for those who had initial VF on or before Feburary 12, 2024, which could occur up to March 4, 2024 (21 days after February 12, 2024) ().

5.4 Analytical Approaches

5.4.1 Analysis of Primary Outcome Measure

Comparison of treatment arms will be made using the difference in the Kaplan-Meier estimate for the week 48 cumulative probability of regimen failure. Specifically, Kaplan-Meier estimates of the 48-week cumulative probabilities of regimen failure and associated Greenwood variance will be calculated. A Z-test and corresponding two-sided confidence interval will then be constructed using the difference between the treatment arms and associated variance of the difference. The final confidence interval will be adjusted for Type I error spent at the interim efficacy analyses and the fact of the randomization and Step 2 follow-up being terminated earlier, to preserve an overall two-sided Type I error rate of 0.05 for the trial. Specifically, a new information fraction will be calculated including additional data from the time of interim analysis data cut to the final analysis data cut. The significance level for the final confidence interval will be recomputed from the O'Brien-Felming spending function at the new information fraction. Analysis will be based on ITT population.

Note: To explore the potential impact of relaxed transition criteria from Step 1 to Step 2 in protocol v.2.0 and v.3.0, characteristics of participants randomized under each protocol version will be compared (Step 2 baseline characteristics and parameters) and primary outcome measures will be tabulated separately.

Supportive Analyses

- Using a modified ITT population. Participants who never started treatment after randomization will be excluded from the analysis.

Subgroup Analyses

To evaluate the effect of the LA-ART compared to oral ART in specific population, the primary outcome measure will be assessed among different subgroups. The same approaches outlined for the primary analysis will be implemented for each subgroup. Within each subgroup, the difference between randomized arms in cumulative probability of regimen failure will be estimated. Comparison between subgroups will be done by a Wald test of the two-way interaction of the randomized arm and the subgroups. In the event that the number of events in a subgroup in either arm is low (less than 5), descriptive summaries by subgroup and arm will be provided. Pre-specified subgroups of interest include:

- Sex at birth: male vs. female
- Race: black vs. no black
- Ethnicity: Hispanic vs. non-hispanic
- Age: < 35 vs. ≥ 35 years
- BMI: < 30 vs. ≥ 30 kg/m^2
- HIV-1 RNA at Step 2 randomization: ≤200 vs. > 200 copies/mL
- CD4 count at Step 2 randomization: ≤200 vs. > 200 counts/mm^3
- Protocol version: v1.0, v2.0 and v3.0

Sensitivity Analyses

- All female participants (regardless of randomized treatment received) who become pregnant without experiencing a virologic failure or permanent discontinuation of study treatment before confirmation of pregnancy will be censored at the study visit week when pregnancy was confirmed.
- Excluding participants found and confirmed to be ineligible for Step 2 if they are included in primary analyses per decision by the team.
- See **Section** Error! Reference source not found. for additional sensitivity analyses for COVID d isruption.

5.4.2 Analysis of Secondary Efficacy Outcome Measures

5.4.2.1 Occurrence of virologic failure in Step 2 [Outcome 10.2.2.1]

Cumulative probability of virologic failure by Step 2, week 48 visit, will be estimated and compared using the same analytical approach (including the sensitivity analyses) outlined for the primary comparison (as described in SAP section 5.4.1).

Supportive Analysis

- Using a modified ITT population. Participants who never started treatment after randomization will be excluded from the analysis.
- Using the as-treated population where a participant's follow-up time will be censored at discontinuation of randomized treatment strategy.

5.4.2.2 Occurrence of the treatment-related failure in Step 2 [Outcome 10.2.2.2]

Cumulative probability of treatment-related failure by Step 2, week 48 visit, will be estimated and compared using the same analytical approach (including the sensitivity analyses) outlined for the primary comparison (as described in SAP section 5.4.1).

Supportive Analysis

- Using a modified ITT population. Participants who never started treatment after randomization will be excluded from the analysis.
- Using the as-treated population where their follow-up time will be censored at discontinuation of randomized treatment strategy.
- Treatment discontinuation due to AE (or death) regardless of relationship to treatment will be used to determine the outcome measure.

5.4.2.3 Virologic non-success defined by FDA Snapshot algorithm[1] at Step 2, week 48 [Outcome 10.2.2.3]

Based on the FDA Snapshot algorithm[1], for switch studies, virologic efficacy should be evaluated as the proportion of participants with HIV-RNA greater than or equal to the limit of quantification at 48 weeks. Hence, virologic failure by FDA Snapshot algorithm is defined as participants who have HIV-RNA levels ≥50 (200) copies/mL in the 48-week window (42 to 54 weeks [295 to 378 days] after Step 2 randomization), discontinued study for other reasons (e.g. lost to follow-up, withdrew consent, etc.) while HIV-1 RNA levels ≥50 (200) copies/mL, or discontinued randomized treatment due to lack of efficacy prior to week 48. The virologic outcome will be determined by the last available measurement while the participant is on treatment and continued on trial within the time window.

The proportion of participants with virologic non-success defined by FDA Snapshot algorithm at Step 2, week 48, will be summarized and compared between the two arms using a Fisher's exact test. The analysis will be based on the ITT population.

If there are no data in the Step 2 week 48 time window (defined above), then percentages for each category of missing data will be tallied:

- *Discontinued due to AE or death*: Any participant who discontinues because of an AE or death before the window will be classified as *Discontinued due to AE or death*, regardless of the HIV-1 RNA result.
- *Discontinued for Other Reasons*: If a participant discontinues the study before the window because of other reasons (e.g. lost to follow-up, withdrew consent, etc.), only participants who have achieved virologic suppression (HIV-1 RNA levels < 50 (200) copies/mL) will be counted as *Discontinued for Other Reasons*. For example, if a participant discontinues because the participant withdrew consent and his or her HIV-1 RNA result at the time of discontinuation was ≥50 (200) copies/mL, then he or she will be categorized as a virologic nonresponse and NOT as *Discontinued for Other Reasons*.
- *On study but missing data in window*: Only data in the window will be used for participants remaining on study. If there are no data during the 48-week window, then the on-study participant will be considered *On study but missing data in window*.

Supportive Analysis

- Using the mITT population.

[1] See Appendix A in "Human Immunodefiniciency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry", U.S. Department of Health and Human Services, FDA CDER, Nov 2015, Clinical/Antimicrobial Revision 1.

5.4.2.4 Plasma HIV-1 RNA level < 50 copies/mL and ≤ 200 copies/mL at scheduled study visits on Step 1 and 2 [Outcome 10.2.2.4]

The proportion of participants with HIV-1 RNA <50 copies/mL and ≤200 copies/mL at each scheduled visit week on Step 1 will be estimated and plotted over time with exact 95% confidence intervals using the Clopper-Pearson method. Similar summaries will be produced for each scheduled visit week on Step 2 by randomized treatment arms and comparison between the two arms at weeks 24 and 48 will use a Fisher's exact test. Analysis will be based on ITT population.

Supportive analyses:

- Using mITT population.
- Using as-treated population.

5.4.2.5 New drug-resistance mutation in participants with virologic failure in Step 2 [Outcome 10.2.2.10]

New HIV-1 drug resistance mutations at virologic failure on Step 2 will be tabulated and the proportion of participants with virologic failure and developed new drug resistant mutations will be compared using a Fisher's exact test between the two treatment arms.

Note: new drug resistant mutations will be based on 2022 IAS update of the Drug Resistance Mutations in HIV-1

5.4.3 Analysis of Safety and Tolerability Outcome Measures

5.4.3.1 Occurrence of adverse event (as defined in protocol section 7.2) during Step 1 and 2 [Outcome 10.2.2.5]

The proportion of participants reporting AEs in Step 2 will be tabulated by MedDRA categorization (SOC and HLT) for each treatment arm. All reported AEs will be tabulated by Steps and separately by randomized treatments for Step 2. Analysis will be based on the mITT population.

Supportive Analyses

- Using an as-treated population. AEs occurring more than 4 weeks after permanent treatment discontinuation will not be included in the analysis.

5.4.3.2 Occurrence of discontinuation of randomized treatment in Step 2 at any time post randomization and week 48 visit [Outcome 10.2.2.6]

Cumulative probability of discontinuation of randomized treatment strategy will be estimated and compared using the same approach outlined for the primary comparison (as described in **Section 5.4.1**). Analysis will be based on ITT population.

Supportive Analyses

- Using the mITT population.

- Per protocol section 10.2.1, switching to another oral ART is not considered treatment discontinuation for participants randomized to SOC arm.

5.4.3.3 Occurrence of Injection Site Reactions (ISR) during Step 2 [Outcome 10.2.2.11]

All grade ISRs will be summarized and tabulated by injection number and by LA-ART during Step 2. Analysis will be based on as-treated population.

NOTE: For clinicaltrials.gov submission, percentage of as-treated population who had at least 1 injection site reaction by LA-ART will be reported.

5.4.4 Analyses of Treatment Satisfaction/Acceptability Outcome Measures

5.4.4.1 Summary score of HIV Treatment Satisfaction Questionnaire (HIVTSQ) in Step 2 [Outcome 10.2.2.7]

Summary score of HIVTSQs will be summarized by treatment arm and compared using a Wilcoxon rank-sum test between arms. Analysis will be based on as-treated population.

5.4.4.2 Summary scores of HIV Treatment Adherence Self-Efficacy Scale in Step 1 and Step 2 [Outcome 10.2.2.9]

Summary scores of HIV Treatment Adherence Self-Efficacy Scale will be summarized by scheduled visit week and separately by randomized treatments for Step 2. Analysis will be based on as-treated population.

5.4.4.3 Paricipants' self-reported opinion (e.g., dissatisfaction) about CEI withdrawal [Other Outcome 10.2.3.8]

Numbers (%) of self-reported opinion categories will be summarized. Analysis will be based on mITT population for Step 1.

5.4.4.4 Participants' self-reported dichotomous preference questionnaire [Outcome 10.2.2.12]

Number (%) of participants' preference will be summarized. Analysis will be based on mITT population.

5.4.5 Analysis of Adherence Outcome Measures

5.4.5.1 Self-reported adherence in Step 1 [10.2.3.9]

Self-reported adherence in Step 1 will be summarized by scheduled visit week. Analysis will be based on as-treated population.

5.4.5.2 Self-reported adherence for participants who randomized to SOC arm in Step 2 [10.2.3.9]

Self-reported adherence for participants who randomized to SOC arm in Step 2 will be summarized by scheduled visit week. Analysis will be based on as-treated population.

5.4.5.3 Occurrence of missed or delayed (defined as 8 days beyond scheduled injection day) injections for participants who received LA ART in Step 2 [Outcome 10.2.2.8]

Missed and delayed LA injection will be summarized by scheduled visit week among those who initiated LA ART. Analysis will be based on as-treated population.

A delayed injection is defined as an injection received 8 days beyond scheduled injection day and less than 56 days from the previous injection.

A missed injection is defined as an injection not received within 56 days from the previous injection.

Note: In addition to missed and delayed LA injections, instances and reasons of oral bridging (temporary switch to oral CAB and/or RPV with study team permission) will also be summarized by scheduled visit week in those who initiated LA ART.

5.4.5.4 Summary scores of substance abuse, health and behavioral-health measures [10.2.3.10]

Substance abuse, health and behvioral-health measures will be summarized at Step 1 and Step 2 baseline. Analysis will be based on mITT population.

5.4.5.5 Summary of socio-demographics measures [10.2.3.11]

Socio-demographic measures will be summarized at Step 1 and Step 2 baseline. Analysis will be based on mITT population.

5.4.5.6 Site Adherence/Retention Measures in Steps 1 and 2 [10.2.3.15]

Site Adherence and retention measures in Steps 1 and 2 will be summarized by Step.

5.4.6 Analysis of additional outcome measures

5.4.6.1 BMI and fasting lipids

Changes from Step 2 entry to Week 48 in BMI and fasting lipids will be summarized and compared by treatment arm. Analysis will be based on mITT population.

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