IMPAACT 2017

Primary Statistical Analysis Plan

Version 3.1

25 August 2023

Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents
"MOCHA"
More Options for Children and Adolescents

ClinicalTrials.gov Identifier: NCT03497676

Protocol Version 4.0, LOA #1

This is IMPAACT 2017 SAP Version 3.0 with names of authors, names of publication writing team members, and analysis timeline redacted.

Table of Contents

TABLE OF CONTENTS **2**

VERSION HISTORY **3**

1 INTRODUCTION **4**
1.1 Purpose **4**
1.2 Version History **4**

2 STUDY OVERVIEW **5**
2.1 Overview of Study Design **5**
2.2 Hypothesis **6**
2.3 Study Objectives **6**
2.3.1 Primary Objective 6
2.3.2 Secondary Objectives 6
2.4 Overview of Sample Size Considerations **7**
2.5 Overview of Formal Interim Monitoring **7**

3 OUTCOME MEASURES **7**
3.1 Primary Outcome Measures **7**
3.2 Secondary Safety and Viral Suppression Outcome Measures **8**

4 ANALYSIS SETS **8**

5 GENERAL CONSIDERATIONS **9**

6 ESTIMANDS AND ANALYSIS **10**
6.1 Primary Estimands and Analysis **10**
6.2 Secondary Estimands and Analysis **12**
6.2.1 Safety Estimands 12
6.2.2 Virologic Estimands 15

7 REPORT CONTENTS **18**

8 ASSOCIATED DOCUMENTS **19**

Version History

Version	Changes Made	Date Finalized
1	Original Version based on Version 2.0 of Protocol	January 22, 2019
2	Updated Version based on Version 3.0 of Protocol. Major changes include: 1. Section 2 was updated to reflect the new treatment regimen in Version 3.0 for both Cohort 1 and Cohort 2, sample size change in Cohort 1, number of dose-evaluable participants required for initial dose-finding evaluation (the first interim analysis), timing of the second interim analysis for opening Cohort 2 to study-naïve participants, and the new secondary objective for viral suppression in Cohort 1. 2. Section 3 was updated to include definitions of Evaluable Population, Cohort 2 Participants with Cohort 1 Experience, and Cohort 2 Participants without Cohort 1 Experience. "Visits and Evaluation Schedule" was removed from Section 4 and put in the AIP, and the new secondary objective for viral suppression in cohort 1 was added in Section 4.	September 3, 2020
3	Updated Version based on Version 4.0 of Protocol. Major changes include: a. Removed references to Cohort 1 analyses. The primary analysis for Cohort 1 was performed using SAP Version 2.0. b. Included all necessary changes from Protocol Version 3.0 to Version 4.0, including the modification of the study design of Cohort 2 to allow the oral lead-in phase to be an optional component of Cohort 2 study participation. i. Modified Cohort 2 to include two groups: Cohort 2A (oral lead-in followed by injections) and Cohort 2B (direct to injections). c. Restructured the SAP to include the following sections: i. Overview of Sample Size Calculations ii. Overview of Formal Interim Monitoring iii. Outcome Measures iv. Estimands and Analysis v. Report Contents	September 6, 2022
3.1	Minor Version change based on LOA #1. No changes needed.	August 25, 2023

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary estimands that will address the Cohort 2 primary and secondary objectives of IMPAACT 2017. The Primary SAP includes general analytic approaches for all estimands and other outcome measures in the primary manuscript(s) or submitted to ClinicalTrials.gov (regardless of the reporting timeline). The Primary SAP facilitates discussion of the statistical analysis components among the lead study investigators and statisticians, helping them agree on the statistical analyses to be performed and presented in the primary analysis report.

It is noted here that all PK analyses, including those required to address the primary and secondary objectives of the study, will be done by the study pharmacologists based on a separate PK SAP (Version 2.0, dated 16 July 2022). In addition, the study's qualitative research team will do the analyses of the data collected through a single qualitative phone interview based on the Qualitative Analysis Plan.

Two primary safety analyses will be performed: (1) after the last participant in Cohort 1 has completed the Week 16 visit and (2) after the last participant in Cohort 2 (A/B) has completed 24/20 weeks on therapy. A secondary safety analysis will be performed after the last participant in Cohort 2 (A/B) has completed 48/44 weeks on therapy. Each primary safety analysis will be done after all queries have been resolved, and the study database closure/data lock has been completed. The primary safety analysis for Cohort 1 will be performed using Version 2.0 of the Primary SAP, dated 3 September 2020. This version of the Primary SAP will focus on the primary and secondary safety outcome measures for Cohort 2. Descriptions of analyses for other objectives and outcome measures not included in this Primary SAP will be provided in a separate SAP.

Detailed outlines of tables, figures, and coding descriptions that will be included in the Cohort 2 primary analysis report(s) are included in the Cohort 2 Analysis Implementation Plan(s) (AIP). As this study will support regulatory submissions, a separate regulatory AIP will be drafted for each regulatory submission.

1.2 Version History

The current Version 3.1 of the IMPAACT 2017 Primary SAP is based on protocol Version 4.0 and Letter of Amendment (LOA) #1.

Version 3.0 of the IMPAACT 2017 Primary SAP is based on protocol Version 4.0. The new version reflects all necessary changes from protocol Version 3.0 to Version 4.0, including the modification of the study design of Cohort 2 to allow the oral lead-in phase to be an optional component of Cohort 2 study participation. To accommodate this, Cohort 2 has been modified to include two groups: Cohort 2A (oral lead-in followed by injections) and Cohort 2B (direct to injections). In addition, references to Cohort 1 were removed, as the primary analysis for Cohort 1 will be performed using Version 2.0 of the Primary SAP. Details of the Cohort 1 primary analysis can be found in Version 2.0.

2 Study Overview

2.1 Overview of Study Design

IMPAACT 2017 is a Phase I/II, multi-center, open-label, non-comparative dose-finding study with the primary objective of evaluating the safety, acceptability, tolerability, and pharmacokinetics of oral cabotegravir (CAB) and long-acting injectable cabotegravir (CAB LA) as well as long-acting injectable rilpivirine (RPV LA) in virologically suppressed children and adolescents living with HIV-1 aged 12 to < 18 years.

The study design includes two cohorts of participants (Cohort 1 and Cohort 2) and five study steps. In Cohort 1 Step 1, participants received either oral CAB or oral RPV for at least 4 weeks and up to 6 weeks (maximum). In Cohort 1 Step 2, participants received injectable formulations of the study products, either CAB LA or RPV LA. Cohort 1 participants were assigned either CAB (Cohort 1C) or RPV (Cohort 1R) based on their pre-study cART regimen, and all participants continued their pre-study cART regimen during Cohort 1.

Cohort 2 participants discontinue their pre-study cART regimen and receive both study products, CAB and RPV, at the doses established in Cohort 1. Cohort 2 participants may enroll to either Cohort 2A to receive both oral CAB + oral RPV (Step 3) followed by both CAB LA + RPV LA (Step 4) or Cohort 2B to directly receive both CAB LA + RPV LA without an oral lead-in phase (Step 5). Unless otherwise specified, the term ‘Cohort 2’ applies to participants in both Cohort 2A and Cohort 2B.

Cohort 2 Treatment under Protocol Version 4.0:

- Cohort 2A (oral lead-in followed by injections): 30 mg CAB + 25 mg RPV once daily orally for at least four weeks, and up to a maximum of 6 weeks, during Step 3 oral phase, followed by intramuscular (IM) injections of CAB LA + RPV LA: first and second injections four weeks apart (CAB LA 600 mg injection + RPV LA 900 mg injection), with subsequent injections every eight weeks through and including Week 96 (CAB LA 600 mg injections + RPV LA 900 mg injections) during Step 4 injection phase.
- Cohort 2B (start with injections): IM injections of CAB LA + RPV LA: first and second injections four weeks apart (CAB LA 600 mg injection + RPV LA 900 mg injection), with subsequent injections every eight weeks through and including Week 92 (CAB LA 600 mg injections + RPV LA 900 mg injections) during Step 5 injection phase.

Participants who prematurely discontinue injectable study product permanently, will continue on-study for an additional 48 weeks after their last study product injection, per the long-term safety and washout PK follow-up (LSFU) schedule.

The sample size for Cohort 2 will be up to 155 adolescents in total. Up to 100 adolescents, who had not previously participated in Cohort 1 (i.e., Cohort 1-naïve), will be enrolled to achieve approximately 70 evaluable. Cohort 2A participants will receive the final recommended oral doses followed by the LA doses of CAB and RPV. Cohort 2B participants will receive the final recommended LA doses of CAB and RPV. Adolescents who participated in Cohort 1 (i.e., Cohort

1 rollovers; up to 55) may continue study participation in Cohort 2, if eligible, in addition to the up to 100 Cohort 2 participants newly enrolled to the study.

At the Week 96/92 visit, Cohort 2A Step 4 and Cohort 2B Step 5 participants continuing to receive injectable CAB LA + RPV LA external to the protocol will exit the study. Section 14.11 of protocol Version 4.0 has more information regarding post-trial access to study products. Participants who discontinue injectable CAB LA + RPV LA at the Week 96/92 visit will not exit the study. These participants will be followed for 48 weeks per the LSFU visit schedule.

2.2 Hypothesis

Cohort 2: The selected dose of CAB LA and RPV LA, when given as dual therapy to stable, virologically suppressed adolescents living with HIV will maintain viral suppression and will be safe through Week 24 (for Cohort 2A oral followed by injectable) and through Week 20 (for Cohort 2B injectable only) in adolescents.

2.3 Study Objectives

2.3.1 Primary Objective

The primary objective for Cohort 2 (discontinuing a background cART regimen) is:

2.3.1.1 To assess the safety of CAB + RPV in adolescents living with HIV who are virologically suppressed through:

- Week 24 (Cohort 2A: oral followed by injectable);
- Week 20 (Cohort 2B: injectable only).

2.3.2 Secondary Objectives

The secondary objectives for Cohort 2 (discontinuing a background cART regimen) are:

2.3.2.1 To assess safety of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:

- Week 48 (Cohort 2A: oral followed by injectable);
- Week 44 (Cohort 2B: injectable only).

2.3.2.2 To evaluate repeat-dose pharmacokinetics of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:

- Week 24 and through Week 48 (Cohort 2A: oral followed by injectable);
- Week 20 and through Week 44 (Cohort 2B: injectable only).

2.3.2.3 To assess antiviral activity of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through:

- Week 24 and through Week 48 (Cohort 2A: oral followed by injectable);
- Week 20 and through Week 44 (Cohort 2B: injectable only).

2.4 Overview of Sample Size Considerations

Details of sample size considerations are provide in Section 9.4 of protocol Version 4.0. Briefly, the sample was driven primarily by safety considerations. **Table 1** below presents exact (Clopper-Pearson) 95% confidence intervals (CI) around various potential rates (0% and 20%) of Grade 3 or higher adverse events (AE) which might be observed in a total sample of 70 participants who enrolled directly into Cohort 2A or 2B (i.e., the primary analysis set for the Cohort 2 safety assessment) as well as for 100 participants who might contribute data to the safety analysis (i.e., all those exposed to the final recommended dose for Cohort 2).

Table 1. Percent of Participants Experiencing Grade 3 or Higher Adverse Events with Exact (Clopper-Pearson) 95% Confidence Intervals.

N	n (%) with Grade 3 of higher Adverse Events	95% CI
70	0 (0%)	0.00, 0.05
100	0 (0%)	0.00, 0.04
70	14 (20%)	0.11, 0.31
100	20 (20%)	0.13, 0.29

2.5 Overview of Formal Interim Monitoring

Interim Analysis #1 took place on 19 June 2020. Based upon study data from the first seven evaluable participants in each Cohort 1C and Cohort 1R, the IMPAACT 2017 CMC concluded that dosing regimens for oral CAB, CAB LA, and RPV LA achieved the PK targets as per protocol Version 2.0. Additionally, the LSFU PK results indicate both CAB and RPV concentrations maintain pharmacologically relevant concentrations, above the IC90, for several weeks after their final IM injection. This interim analysis confirmed that the doses implemented for both Cohort 1C and Cohort 1R passed the safety guidelines in Section 9.5.1.3 of protocol Version 2.0 for the first seven evaluable participants in each group. The CMC concluded that protocol criteria to open Cohort 2 to Cohort 1 graduates had been met, and the SMC agreed with this conclusion.

Interim Analysis #2 was conducted on 18 April 2022. The doses implemented for both Cohort 1C and Cohort 1R passed the safety guidelines per Section 9.5.1.3 of protocol Version 3.0. The CMC concluded that the analysis supported opening Cohort 2 accrual to participants who were not previously enrolled in Cohort 1, and the SMC agreed with this conclusion.

A final analysis of Cohort 1 data will be performed to confirm the final doses for Cohort 2 (using Version 2.0 of the Primary SAP).

3 Outcome Measures

3.1 Primary Outcome Measures

Safety through Week 24 (Cohort 2A)/through Week 20 (Cohort 2B):

- Any adverse event, regardless of grade
- Grade 3 or higher adverse event
- Grade 3 or higher adverse event assessed as related to study product(s)
- Serious adverse event meeting ICH criteria assessed as related to study product(s)
- Permanent discontinuation of study product due to adverse event assessed as related to study product(s)
- Death due to adverse event assessed as related to study product(s)

3.2 Secondary Safety and Viral Suppression Outcome Measures

Safety through Week 48 (Cohort 2A)/through Week 44 (Cohort 2B):

- Any adverse event, regardless of grade
- Grade 3 or higher adverse event
- Grade 3 or higher adverse event assessed as related to study product(s)
- Serious adverse event meeting ICH criteria assessed as related to study product(s)
- Permanent discontinuation of study product due to adverse event assessed as related to study product(s)
- Death due to adverse events assessed as related to study product(s)

Virologic activity through Week 24 and through Week 48 (Cohort 2A)/through Week 20 and through Week 44 (Cohort 2B):

- Plasma HIV-1 RNA ≥50 copies/mL, per snapshot algorithm
- Plasma HIV-1 RNA ≥200 copies/mL, per snapshot algorithm

NOTE: PK outcome measures are described in the PK SAP.

4 Analysis Sets

The following analysis sets are defined:

All Treated: All participants who took at least one dose of any study product in Cohort 2

Evaluable: For analysis purposes, evaluable participants will be defined as having been treated exclusively on the final recommended dose and either (1) having completed all treatment regimen through Week 24 (Cohort 2A)/Week 20 (Cohort 2B) or (2) having experienced any of the following:

- death that is attributable to the study product(s), OR
- study product-related Grade 3 or higher event (excluding injection-site AEs), OR
- permanently discontinued from treatment due to study product-related toxicities (regardless of grade) during these weeks of treatment.

Notes:

- An additional requirement for inclusion in the primary analyses for Cohort 2 is that the participants must be directly accrued to this cohort and be exclusively treated with the combination of the two study products; this will be approximately 70 participants.

- Oral bridging in Cohort 2 will not be counted as a substitute for an injection but as long as the recommended number of injections were given through Week 24/Week 20, even if they were out of window, the participantwill be considered evaluable.

Cohort 1 Rollover: Cohort 2 participants who were previously enrolled to Cohort 1.

Cohort 1-Naïve: Cohort 2 participants who were enrolled directly to Cohort 2 without prior participation in Cohort 1.

5 General Considerations

The derivation of PK parameters will be performed by the IMPAACT 2017 protocol pharmacologists, as described in the PK SAP. The statistical summaries to be prepared by the statisticians are described in this Primary SAP.

Continuous variables will be summarized by N, N missing, mean, standard deviation, and quantiles of minimum, 25th percentile, median, 75th percentile, and maximum. Categorical variables will be summarized by N (%) in each category, excluding the missing category in the denominator.

For all baseline demographics and exposure analyses, results will be presented for the All Treated analysis set. The baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. Unless otherwise stated, if baseline data are missing, no derivation will be performed and baseline will be set to missing.

All safety data will be considered from the first patient exposure to study treatment. Each participant's safety data will be summarized as: (1) the worst grade of each AE and (2) the worst grade of each AE judged to be related to study treatment.

Listings of all Grade 3 or higher AEs regardless of treatment attribution, serious AEs meeting ICH criteria assessed as related to study product(s), and AEs which resulted in permanent discontinuation of study product(s) or death will be provided. These categories of AEs will also be summarized and broken down by System Organ Class. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study. This table is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Analyses of primary and secondary outcome measures will include Cohort 1-naïve evaluable participants, as defined above. Supplementary analyses of safety and virologic outcome measures will include all participants (Cohort 1-naïve and Cohort 1 rollovers) who received study products (All Treated analysis set referenced above).

6 Estimands and Analysis

6.1 Primary Estimands and Analysis

<table>
<tr><td colspan="3">Primary Objective 1: To assess the safety of CAB + RPV in adolescents living with HIV who are virologically suppressed through Week 24 (Cohort 2A)/Week 20 (Cohort 2B).</td></tr>
<tr><td>Estimand</td><td colspan="2">Probability of a virologically suppressed adolescent (aged 12 to <18 years) living with HIV-1, who was either exclusively treated with the combination of RPV and CAB at the final recommended dose for 24 weeks (for oral lead-in) or 20 weeks (for direct to injection), experienced a severe, potentially life-threatening, or death event attributable to CAB and/or RPV, or permanently discontinued CAB and/or RPV due to a related toxicity, having at least one event (any adverse event; severe, potentially life-threatening, or death event; severe, potentially life-threatening, or death event assessed as related to CAB and/or RPV; serious adverse event assessed as related to CAB and/or RPV; permanent discontinuation of CAB and/or RPV due to adverse event assessed as related to CAB and/or RPV; death due to adverse event assessed as related to CAB and/or RPV).</td></tr>
<tr><td>Treatment</td><td colspan="2">30 mg CAB + 25 mg RPV once daily orally for four weeks followed by IM injections of 600 mg CAB LA + 900 mg RPV LA (first and second injections four weeks apart with subsequent injections every eight weeks) or direct to IM injections of 600 mg CAB LA + 900 mg RPV LA (first and second injections four weeks apart with subsequent injections every eight weeks).</td></tr>
<tr><td>Target population</td><td colspan="2">Analysis set</td></tr>
<tr><td>Virologically suppressed children and adolescents 12 to <18 years of age living with HIV-1 exclusively treated with the combination of RPV and CAB at the final recommended dose for either 24 weeks (for oral lead-in) or 20 weeks (for direct to injection).</td><td colspan="2">Participants who are exclusively treated with the combination of RPV and CAB at the final recommended dose and either completed all treatment regimen through the Week 24 (Cohort 2A)/Week 20 (Cohort 2B) visit or experienced any of the following:
death that is attributable to the study product(s), OR
study product-related Grade 3 or higher adverse event (excluding injection-site AEs), OR
permanent discontinuation from treatment due to study product-related toxicities (regardless of grade) during these weeks of</td></tr>
</table>

	treatment.
Variable(s)	Outcome measure(s)
Occurrence of each of the following through 24 weeks (for oral lead-in) or 20 weeks (for direct to injection): • Any adverse event • Severe, potentially life-threatening, or death event • Severe, potentially life-threatening, or death event assessed as related to CAB and/or RPV • Serious adverse event related to CAB and/or RPV • Permanent discontinuation of CAB and/or RPV due to adverse event assessed as related to CAB and/or RPV • Death due to adverse event assessed as related to CAB and/or RPV	Occurrence of each of the following through Week 24 (Cohort 2A)/through Week 20 (Cohort 2B): • Any adverse event, regardless of grade • Grade 3 or higher adverse event • Grade 3 or higher adverse event assessed as related to study product(s) • Serious adverse event meeting ICH criteria assessed as related to study product(s) • Permanent discontinuation of study product due to adverse event assessed as related to study product(s) • Death due to adverse event assessed as related to study product(s)
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: 1. Discontinuation of CAB and/or RPV due to toxicity 2. Death related to CAB and/or RPV These intercurrent events (1, 2) will be addressed using a while on treatment strategy. 3. Discontinuation of CAB and/or RPV due to non-toxicity reasons 4. Death unrelated to CAB and/or RPV These intercurrent events (3, 4) will be addressed using a principal stratum approach.	Missing data will be addressed using a “complete case” approach, defined per outcome measure.
Population-level summary measure	Analysis approach
Probability of having at least one event (any adverse event; severe, potentially life-threatening, or death event; severe, potentially	Proportion of participants with at least one event (any adverse event; Grade 3 or higher adverse event; Grade 3 or higher

life-threatening, or death event assessed as related to CAB and/or RPV; serious adverse event assessed as related to CAB and/or RPV; permanent discontinuation of CAB and/or RPV due to adverse event assessed as related to CAB and/or RPV; death due to adverse event assessed as related to CAB and/or RPV) through 24 weeks (for oral lead-in) or 20 weeks (for direct to injection).	adverse event assessed as related to study product(s); serious adverse event meeting ICH criteria assessed as related to study product(s); permanent discontinuation of study product due to adverse event assessed as related to study product(s); death due to adverse event assessed as related to study product(s)) through Week 24 (Cohort 2A)/through Week 20 (Cohort 2B), bounded by an exact (Clopper-Pearson) 95% CI.

Sensitivity Analyses

Because complete case approach assumes data are missing completely at random, we will use multiple imputation that assumes missing at random as a sensitivity analysis. We will create 100 imputed data sets using appropriate fully conditional specified (FCS) model and combine results using Rubin's rules. We will also present estimates assuming "best case" (i.e., probability of event = 0) and "worst case" (i.e., probability of event = 1) scenarios. Of note, only participants who are deemed evaluable will be included in this primary analysis; therefore, very little (if any) missing data is expected. Sensitivity analyses related to missing data in the All Treated analysis set will be addressed in the supplementary analyses.

Supplementary Analyses

Supplementary analyses for the primary outcome measures will include all participants (Cohort 1-naïve and Cohort 1 rollovers) who received study products. All intercurrent events will be addressed using a while on treatment strategy, and missing data will be handled using a complete case approach. Because this approach assumes data are missing completely at random, we will use multiple imputation that assumes missing at random as a sensitivity analysis. We will create 100 imputed data sets using appropriate FCS model and combine results using Rubin's rules. We will also present estimates assuming "best case" (i.e., probability of event = 0) and "worst case" (i.e., probability of event = 1) scenarios.

6.2 Secondary Estimands and Analysis

6.2.1 Safety Estimands

Secondary Objective 1: To assess the safety of CAB + RPV in adolescents living with HIV who are virologically suppressed through Week 48 (Cohort 2A)/Week 44 (Cohort 2B).	
Estimand	Probability of a virologically suppressed adolescent (aged 12 to <18 years) living with HIV-1, who was either exclusively treated with the combination of RPV and CAB at the final recommended dose for 48 weeks (for oral lead-in) or 44 weeks (for direct to injection), experienced a severe, potentially life-threatening, or death event attributable to CAB and/or RPV, or permanently

	discontinued CAB and/or RPV due to a related toxicity, having at least one event (any adverse event; severe, potentially life-threatening, or death event; severe, potentially life-threatening, or death event assessed as related to CAB and/or RPV; serious adverse event assessed as related to CAB and/or RPV; permanent discontinuation of CAB and/or RPV due to adverse event assessed as related to CAB and/or RPV; death due to adverse event assessed as related to CAB and/or RPV).
Treatment	30 mg CAB + 25 mg RPV once daily orally for four weeks followed by IM injections of 600 mg CAB LA + 900 mg RPV LA (first and second injections four weeks apart with subsequent injections every eight weeks) or direct to IM injections of 600 mg CAB LA + 900 mg RPV LA (first and second injections four weeks apart with subsequent injections every eight weeks).

Target population	Analysis set
Virologically suppressed children and adolescents 12 to <18 years of age living with HIV-1 exclusively treated with the combination of RPV and CAB at the final recommended dose for either 48 weeks (for oral lead-in) or 44 weeks (for direct to injection).	Participants who are exclusively treated with the combination of RPV and CAB at the final recommended dose and either completed all treatment regimen through the Week 48 (Cohort 2A)/Week 44 (Cohort 2B) visit or experienced any of the following: • death that is attributable to the study product(s), OR • study product-related Grade 3 or higher adverse event (excluding injection-site AEs), OR • permanent discontinuation from treatment due to study product-related toxicities (regardless of grade) during these weeks of treatment.
Variable(s)	**Outcome measure(s)**
Occurrence of each of the following through 48 weeks (for oral lead-in) or 44 weeks (for direct to injection): • Any adverse event • Severe, potentially life-threatening, or death event • Severe, potentially life-threatening, or death event assessed as related to CAB and/or RPV	Occurrence of each of the following through Week 48 (Cohort 2A)/through Week 44 (Cohort 2B): • Any adverse event, regardless of grade • Grade 3 or higher adverse event • Grade 3 or higher adverse event assessed as related to study product(s)

• Serious adverse event related to CAB and/or RPV • Permanent discontinuation of CAB and/or RPV due to adverse event assessed as related to CAB and/or RPV • Death due to adverse event assessed as related to CAB and/or RPV	• Serious adverse event meeting ICH criteria assessed as related to study product(s) • Permanent discontinuation of study product due to adverse event assessed as related to study product(s) • Death due to adverse event assessed as related to study product(s)
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: 1. Discontinuation of CAB and/or RPV due to toxicity 2. Death related to CAB and/or RPV These intercurrent events (1, 2) will be addressed using a while on treatment strategy. 3. Discontinuation of CAB and/or RPV due to non-toxicity reasons 4. Death unrelated to CAB and/or RPV These intercurrent events (3, 4) will be addressed using a principal stratum approach.	Missing data will be addressed using a "complete case" approach, defined per outcome measure.
Population-level summary measure	Analysis approach
Probability of having at least one event (any adverse event; severe, potentially life-threatening, or death event; severe, potentially life-threatening, or death event assessed as related to CAB and/or RPV; serious adverse event assessed as related to CAB and/or RPV; permanent discontinuation of CAB and/or RPV due to adverse event assessed as related to CAB and/or RPV; death due to adverse event assessed as related to CAB and/or RPV) through 48 weeks (for oral lead-in) or 44 weeks (for direct to injection).	Proportion of participants with at least one event (any adverse event; Grade 3 or higher adverse event; Grade 3 or higher adverse event assessed as related to study product(s); serious adverse event meeting ICH criteria assessed as related to study product(s); permanent discontinuation of study product due to adverse event assessed as related to study product(s); death due to adverse event assessed as related to study product(s)) through Week 48 (Cohort 2A)/through Week 44 (Cohort 2B), bounded by an exact (Clopper-Pearson) 95% CI.

Sensitivity Analyses

Because complete case approach assumes data are missing completely at random, we will use multiple imputation that assumes missing at random as a sensitivity analysis. We will create 100 imputed data sets using appropriate FCS model and combine results using Rubin's rules. We will also present estimates assuming "best case" (i.e., probability of event = 0) and "worst case" (i.e., probability of event = 1) scenarios. Of note, only participants who are deemed evaluable will be included in this primary analysis; therefore, very little (if any) missing data is expected. Sensitivity analyses related to missing data in the All Treated analysis set will be addressed in the supplementary analyses.

Supplementary Analyses

Supplementary analyses for the secondary safety outcome measures will include all participants (Cohort 1-naïve and Cohort 1 rollovers) who received study products. All intercurrent events will be addressed using a while on treatment strategy, and missing data will be handled using a complete case approach. Because this approach assumes data are missing completely at random, we will use multiple imputation that assumes missing at random as a sensitivity analysis. We will create 100 imputed data sets using appropriate FCS model and combine results using Rubin's rules. We will also present estimates assuming "best case" (i.e., probability of event = 0) and "worst case" (i.e., probability of event = 1) scenarios, as a sensitivity analysis.

6.2.2 Virologic Estimands

Secondary Objective 3: To assess antiviral activity of CAB LA + RPV LA in adolescents living with HIV who are virologically suppressed through Week 24 and through Week 48 (Cohort 2A: oral followed by injectable)/through Week 20 and through Week 44 (Cohort 2B: injectable only).	
Estimand	Probability of a virologically suppressed adolescent (aged 12 to <18 years) living with HIV-1, who was either exclusively treated with the combination of RPV and CAB at the final recommended dose for 24 weeks (for oral lead-in) or 20 weeks (for direct to injection), experienced a severe, potentially life-threatening, or death event attributable to CAB and/or RPV, or permanently discontinued CAB and/or RPV due to a related toxicity, having virologic failure (plasma HIV-1 RNA ≥50 copies/mL; plasma HIV-1 RNA ≥200 copies/mL) through 24/48 weeks (for oral lead-in) or 20/44 weeks (for direct to injection).
Treatment	30 mg CAB + 25 mg RPV once daily orally for four weeks followed by IM injections of 600 mg CAB LA + 900 mg RPV LA (first and second injections four weeks apart with subsequent injections every eight weeks) or direct to IM injections of 600 mg CAB LA + 900 mg RPV LA (first and second injections four weeks apart with subsequent injections every eight weeks).
Target population	Analysis set

Virologically suppressed children and adolescents 12 to <18 years of age living with HIV-1 exclusively treated with the combination of RPV and CAB at the final recommended dose for either 24/48 weeks (for oral lead-in) or 20/44 weeks (for direct to injection).	Participants who are exclusively treated with the combination of RPV and CAB at the final recommended dose and either completed all treatment regimen through the Week 24/48 (Cohort 2A)/Week 40/44 (Cohort 2B) visit or experienced any of the following: • death that is attributable to the study product(s), OR • study product-related Grade 3 or higher adverse event (excluding injection-site AEs), OR • permanent discontinuation from treatment due to study product-related toxicities (regardless of grade) during these weeks of treatment.
Variable(s)	Outcome measure(s)
Occurrence of virologic failure through 24/48 weeks (oral lead in)/through 20/44 weeks (direct to injection): • Plasma HIV-1 RNA ≥50 copies/mL • Plasma HIV-1 RNA ≥200 copies/mL	Occurrence of virologic failure through Week 24 and through Week 48 (Cohort 2A)/through Week 20 and through Week 44 (Cohort 2B): • Plasma HIV-1 RNA ≥50 copies/mL, per snapshot algorithm • Plasma HIV-1 RNA ≥200 copies/mL, per snapshot algorithm
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: 1. Discontinuation of CAB and/or RPV due to toxicity 2. Death related to CAB and/or RPV These intercurrent events (1, 2) will be addressed as specified in the snapshot algorithm. 3. Discontinuation of CAB and/or RPV due to non-toxicity reasons	Missing data will be handled as described in the snapshot algorithm.

4. Death unrelated to CAB and/or RPV These intercurrent events (3, 4) will be addressed using a principal stratum approach.	
Population-level summary measure	Analysis approach
Probability of virologic failure (plasma HIV-1 RNA ≥50 copies/mL; plasma HIV-1 RNA ≥200 copies/mL) through 24/48 weeks (for oral lead-in) or 20/44 weeks (for direct to injection).	Proportion of participants with virologic failure (plasma HIV-1 RNA ≥50 copies/mL, per snapshot algorithm; plasma HIV-1 RNA ≥200 copies/mL, per snapshot algorithm) through Week 24/48 (Cohort 2A)/through Week 40/44 (Cohort 2B), bounded by an exact (Clopper-Pearson) 95% CI.

Sensitivity Analyses

Lower Limit of Quantification

To correspond with the Cohort 1 primary analysis, results in the form of "< Lower Limit of Quantification" will be imputed as lower limit of quantification (LLoQ) – 1. For HIV-1 RNA results where the LLoQ is greater than the cut-off value (e.g., 60 copies/mL), we will perform four sensitivity analyses:

(1) impute all values as < cut-off value,
(2) multiply impute plasma RNA HIV-1 values using a uniform distribution (1 to LLoQ),
(3) set values to missing,
(4) impute values as < cut-off value if the target was not detected in the assay and set values to missing if the target was detected.

Missing Data

Because the snapshot algorithm is a single imputation method that includes a "No virologic data" category (i.e., data can still be missing), we will use multiple imputation that assumes missing at random as a sensitivity analysis. We will create 100 imputed data sets using appropriate FCS model and combine results using Rubin's rules. We will also present estimates assuming "best case" (i.e., probability of event = 0) and "worst case" (i.e., probability of event = 1) scenarios, as a sensitivity analysis. Of note, we will impute whether the participant was < or ≥ the cut-off value (50 or 200), not the plasma RNA HIV-1 value, for missing study visits prior to implementing the snapshot algorithm.

Supplementary Analyses

Supplementary analyses for the secondary virologic outcome measures will include all participants (Cohort 1-naïve and Cohort 1 rollovers) who received study products. All intercurrent

events and missing data will be handled as described in the snapshot algorithm. The sensitivity analyses described above will be implemented.

7 Report Contents

This section lists the major report contents that may be included the Primary Analysis Reports. Detailed descriptions of the content of each of the following sections are given in the AIP.

1 Introduction
2 Background
- I. Study Design
- II. Objectives
- III. Outcome Measures
- IV. Study History and Monitoring History

3 Statistical Considerations
- I. Analysis Populations
- II. General Considerations
- III. Estimands and Estimation

4 Disposition
- I. CONSORT Diagram
- II. Screening
- III. Accrual
- IV. Protocol Deviations
- V. Evaluability

5 Baseline Characteristics
6 Study Status and Retention
7 Status of Drugs under Study
8 Primary Analyses
9 Secondary Analyses
10 Other Analyses
11 Summary

8 Associated Documents

Attachment 1: Writing Team Roster

Attachment 2: Snapshot Algorithm (using cut-off of HIV-1 RNA 200 copies/mL)

Condition ('Week 24' indicates Week 24 window/'Week 20' indicates Week 20 window)	**Response**	**Reasons**
1. If ***non-permitted*** change in background therapy ***prior to*** Week 24/Week 20	HIV1-RNA ≥ 200	Change in ART
2. If ***permitted*** change in background therapy ***prior to*** Week 24/Week 20 AND the latest on-treatment VL prior to/on the date of change is ≥ 200 copies/mL	HIV1-RNA ≥ 200	Change in ART
3. If ***non-permitted*** change in background therapy ***during*** Week 24/Week 20		
• Last on-treatment VL during Week 24/Week 20 prior to/on the date of change ≥ 200 copies/mL	HIV1-RNA ≥ 200	Data in window and HIV-1 RNA ≥ 200 copies/mL
• Last on-treatment VL during Week 24/Week 20 prior to/on the date of change <200 copies/mL	HIV1-RNA < 200	
• No VL during Week 24/Week 20 prior to/on the date of change	HIV1-RNA ≥ 200	Change in ART
4. If ***permitted*** change in background therapy ***during*** Week 24/Week 20 AND the last on-treatment VL prior to/on the date of change is ≥ 200 copies/mL		
4.1 This last on-treatment VL occurs prior to Week 24/Week 20	HIV1-RNA ≥ 200	Change in ART
4.2 This last on-treatment VL occurs during Week 24/Week 20 but prior to/on the date of change	HIV1-RNA ≥ 200	Data in window and HIV-1 RNA ≥ 200 copies/mL
5. If none of the above conditions met		
5.1 VL available during Week 24/Week 20		
• Last on-treatment VL during Week 24/Week 20 ≥ 200 copies/mL	HIV1-RNA ≥ 200	Data in window and HIV-1 RNA ≥ 200 copies/mL
• Last on-treatment VL during Week 24/Week 20 < 200 copies/mL	HIV1-RNA < 200	
5.2 No VL during Week 24		
• If subjects still on study (i.e. IP has not been permanently stopped up to Week 24)	No virologic data at Week 24 Window	On study but missing data in window
• If subjects withdraw before/during Week 24 due to		

– Safety reasons (e.g. AE/death, liver chemistry stopping criteria, renal toxicity withdrawal criteria, QTc withdrawal criteria et al, as recorded in eCRF Conclusion form)	No virologic data at Week 24 Window	Disc due to AE/death
– Non-safety related reasons (e.g. Lack of efficacy, protocol deviation, withdrew consent, loss to follow-up, study closed/terminated, investigator discretion et al, as recorded in eCRF Conclusion Form)		
o Last on-treatment VL <200 c/mL OR no on-treatment VL available during study	No virologic Data at Week 24 Window	Disc for other reasons
o Last on-treatment VL ≥ 200 c/mL AND withdrawal due to Lack of efficacy	HIV1-RNA ≥ 200	Disc. for lack of efficacy
o Last on-treatment VL ≥ 200 c/mL AND withdrawal due to all other non-safety related reasons	HIV1-RNA ≥ 200	Dis. for other reason and HIV-1 RNA ≥ 200 copies/mL

Note the same process will be mapped out for Week 48.

Examples from FDA guidance (cut-off of 50 copies/mL):

Data in Window

Virologic outcome should be determined by the last available measurement while the patient is on treatment and continued on trial within the time window:

HIV-RNA = 580 copies/mL at Day 336, HIV-RNA below 50 copies/mL on Day 350. This should be categorized as HIV-RNA below 50 copies/mL.

No Data in Window

Discontinued study due to Adverse Event or Death:

Any patient who discontinues because of an AE or death before the window should be classified as Discontinued due to AE or Death (as appropriate), regardless of the HIV-RNA result, even if the HIV-RNA is below 50 copies/mL at the time of discontinuation.

However, if a patient has an HIV-RNA value in the time window and also discontinues in the time window, the viral load data should be used to classify the patient's response. This is the Virology First hierarchy:

HIV-RNA below 50 copies/mL at Day 336 and discontinues because of AE or even dies on Day 360 — this person is categorized as having HIV-RNA below 50 copies/mL.

HIV-RNA is 552 copies/mL on Day 336 and the patient discontinues on Day 360, the patient is categorized as having HIV-RNA greater than or equal to 50 copies/mL.

Discontinued for Other Reasons:

Only patients who have achieved virologic suppression can be counted as Discontinued for Other Reasons.

If a patient discontinues the study before the window because of lack of efficacy then the patient should be included in the HIV-RNA greater than or equal to 50 row and not in the Discontinued for Other Reasons row.

If a patient discontinues because of subject withdrew consent and his or her HIV-1 RNA result at the time of discontinuation was equal to or above 50 copies/mL, then he or she should be categorized as HIV-RNA greater than or equal to 50 and NOT as Discontinued for Other Reasons.

If a patient discontinued because of Lost to Follow-Up and the last HIV-RNA result was 49 copies/mL, then the patient can be categorized as Discontinued for Other Reasons.

If patients changed background treatment — not permitted by protocol— they should be considered an efficacy failure and captured in the HIV-RNA greater than or equal to 50 copies/mL row.

On study but missing data in window:

If there are no data during Days 294 to 377, but there is an HIV-RNA below 50 copies/mL on Day 380, this patient should be considered On Study but Missing Data in Window.

If there are no data during Days 294 to 377, but there is an HIV-RNA equal to or above 50 copies/mL on Day 280, this patient also should be classified as On Study but Missing Data in Window.