FINAL

IMPAACT 2017
Primary Statistical Analysis Plan

Version 2.0

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

Protocol Version 3.0

Clinical Trials.gov Identifier: NCT03497676

September 3, 2020

This is IMPAACT 2017 SAP Version 2.0 with names of authors, names of publication writing team members, and analysis timeline redacted.

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1. Introduction

Purpose and Reporting Timelines

This Primary Statistical Analysis Plan (SAP) describes analyses that address the primary and secondary objectives of IMPAACT 2017 that will be included in the primary manuscript. The Primary SAP outlines the general statistical approaches that will be used in the analysis. 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 Statistical Analysis Reports. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov.

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 Analysis Plan. 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 has completed 24 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 Statistical Analysis Reports will be used for submission of results to ClinicalTrials.gov. Results for primary outcomes are required to be submitted within one year of the primary completion date (PCD), which is the date the last participant is examined for the purposes of data collection for the primary outcome measure. For this study, the PCD is the date of the Week 24 visit for the last participant in Cohort 2. At the end of the study, a second submission to ClinicalTrials.gov will be done within one year after the last Cohort 2 participant reaches Week 144 (treatment through Week 96 plus 48 weeks of long-term safety and washout PK follow-up) at which time point the adverse event tables will be updated.

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

1.1 Key SAP Updates

Version	Changes Made	Effective Date
1	Original Version based on Version 2.0 of Protocol	01/22/2019
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. 3. "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.	09/03/2020

2. Protocol Overview

2.1 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 CAB and CAB LA as well as RPV LA in virologically suppressed HIV-1 infected children and adolescents 12 to < 18 years of age.

There will be two cohorts of participants and two steps of study participation in each cohort. Cohort 1 Step 1 and Cohort 2 Step 3 are both a lead-in phase in which participants will receive oral formulations of the study products for at least 4 weeks, and up to 6 weeks (maximum). In Cohort 1 Step 2 and Cohort 2 Step 4, participants will receive injectable formulations of the study products. There will be two groups under Cohort 1: Cohort 1C and Cohort 1R. The study products are listed as follows. Note that since 23 participants were enrolled to Cohort 1 under Protocol Version 2.0, Cohort 1 treatments under Protocol Version 2.0 are also listed. Since no participant was enrolled to Cohort 2 under Version 2.0, Cohort 2 treatment under Protocol Version 2.0 is not applicable/included.

Cohort 1 Treatment under Protocol Version 2.0:

- Cohort 1C: 30 mg CAB once daily orally for at least four weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 oral phase), followed by single intramuscular injections of CAB LA every

four weeks over an eight-week period (600 mg first injection, 400 mg second and third injections) in addition to cART (Step 2 injection phase).

- Cohort 1R: 25 mg RPV once daily orally for at least four weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 oral phase), followed by single intramuscular injections of RPV LA every four weeks over an eight-week period (900 mg first injection, 600 mg second and third injections) in addition to cART (Step 2 injection phase).

Cohort 1 Treatment under Protocol Version 3.0:

- Cohort 1C: 30 mg CAB once daily orally for at least four weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 oral phase), followed by two single intramuscular injections of CAB LA four weeks apart (600 mg injections) in addition to cART (Step 2 injection phase).
- Cohort 1R: 25 mg RPV once daily orally for at least four weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 oral phase), followed by two single intramuscular injections of RPV LA four weeks apart (900 mg injections) in addition to cART (Step 2 injection phase).

Cohort 2 Treatment under Protocol Version 3.0:

- 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 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.

In each cohort, participants will enter the study in the oral lead-in phase (Step 1, or Step 3) and then transition to the injectable phase (Step 2, or Step 4) if eligibility criteria for the injectable phase are met. Cohort 1 Step 2 and Cohort 2 Step 4 participants, including those who prematurely permanently discontinue injectable study product, 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 will be up to 155 adolescents in total, broken down as follows:

Cohort 1: Up to 55 adolescents to achieve approximately 30 to 35 dose-evaluable receiving the oral followed by the LA dose of CAB (Cohort 1C) or RPV (Cohort 1R), in addition to the background cART.

- Cohort 1C: Up to 30 adolescents to achieve approximately 15 to 20 dose-evaluable for CAB.
- Cohort 1R: Up to 25 adolescents to achieve approximately 15 dose-evaluable for RPV.

The dose-evaluable population for each group will include at least 4 female adolescents, at least 4 male adolescents, at least 5 adolescents weighing 35 kg to less than 50 kg at study entry, and at least 5 adolescents weighing at least 50 kg at study entry.

Cohort 2: Up to 155 adolescents may participate in Cohort 2. Up to 100 adolescents, who had not previously participated in Cohort 1, will be enrolled to achieve approximately 70 evaluable who had not previously participated in Cohort 1. The Cohort 2 participants will receive the final recommended oral doses followed by the LA doses of CAB and RPV. Adolescents who participated in Cohort 1 (up to 55 participants) may continue study participation in Cohort 2, if eligible, in addition to the up to 100 Cohort 2 participants newly enrolled to the study.

For the qualitative component of the study, up to 60 adolescent participants and up to 60 parents or caregivers of adolescent participants will be selected by the qualitative team to complete a single qualitative phone interview (U.S. sites only).

In Step 1, data collected through Week 4 (Week 4a and Week 4b study visits) for Cohort 1 participants will be assessed to determine eligibility for each participant to enter Step 2 and receive injectable CAB LA in Cohort 1C or RPV LA in Cohort 1R, respectively. Cohort 1 participants who do not meet eligibility criteria for Step 2 will discontinue use of oral CAB or RPV and exit the study 28 days after their last oral study product dosing.

In Step 2, participants will receive CAB LA (Cohort 1C) or RPV LA (Cohort 1R) while continuing their cART regimen. A single intramuscular (IM) injection of CAB LA or RPV LA will be administered at the Week 4b (Step 2 Entry), Week 8, and Week 12 for participants enrolled under Version 2.0, and at the Week 4b (Step 2 Entry) and Week 8 for participants enrolled under Version 3.0. Cohort 1 Step 2 participants will be followed for safety and PK assessments through their Week 16 visit.

Once seven dose-evaluable Cohort 1C participants and seven dose-evaluable Cohort 1R participants have completed injectable study product dosing in Step 2, and have completed safety and PK evaluations through the Cohort 1 Step 2 Week 16 visit, the first interim safety and PK analysis will be performed to:

- Determine whether criteria have been met to open Cohort 2 to accrual — limited to Cohort 1 participants
- Determine the doses of the oral and injectable CAB study products, and the injectable RPV study product to be provided in Cohort 2

If the seven dose-evaluable participants in each group meet the PK guidelines (see Section 10 of the protocol) and there are no safety concerns (see Section 9 of the protocol), then the oral/LA IM doses for CAB and LA IM dose for RPV in Cohort 2 will be established and Cohort 2 will begin to accrue, but only for Cohort 1 participants who completed the Week 16 visit.

If either group fails the safety or PK criteria and an alternative dose is determined by the study team to be needed to safely achieve necessary study product concentrations, another seven dose-evaluable participants will be enrolled into that group and administered a modified dose which will be evaluated as described above.

If there is more variability than expected in the PK results in each or both groups of Cohort 1, such that a confident determination regarding achievement of the PK targets cannot be made, an additional interim evaluation of the PK results will be done after an additional four participants have been enrolled into the appropriate group/s of Cohort 1 to clarify the PK results as needed. In this scenario, Cohort 2 accrual will be delayed until an interim analysis which includes these extra participants has been reviewed and Cohort 2 dosing is confirmed by the study team. In this case, the safety evaluation criteria will be such that failure would consist of either: 1) a death or life-threatening toxicity assessed as related to the study drug or 2) more than 25% of the sample having exhibited Grade 3+ toxicities assessed to be related to the study drug.

Additional interim analysis of the PK results may also be performed if any of the study cohorts fails the safety criteria, which would trigger an SMC review.

Cohort 1 study enrollment and study procedures will not be interrupted for the interim analysis to be performed on the first seven participants enrolled into each group.

Once approximately 15-20 Cohort 1C participants and approximately 15 Cohort 1R participants contributing to the dose-finding algorithm have enrolled, and 80% of these participants have completed the Step 2 Week 8 visit, the second interim analysis of all available safety and PK data will be conducted to determine if Cohort 2 accrual can be opened to study-naïve participants. Once all Cohort 1C and 1R participants complete Week 16 visit, the final analysis of all safety and PK data for Cohort 1 will be conducted to confirm the oral and LA IM doses for Cohort 2.

Upon enrollment into Cohort 2, participants will discontinue their pre-study cART regimen and receive oral CAB+RPV for at least 4 weeks (and up to 6 weeks) in Step 3. Data collected through the Week 4 (Week 4a and Week 4b study visits) will be assessed to determine eligibility for each participant to enter Step 4 and receive injectable CAB LA + RPV LA.

Cohort 2 participants who meet eligibility criteria for Step 4 will receive their last oral dose of CAB+RPV on the same day as their first injection of CAB LA + RPV LA, at the Week 4b Step 4 Entry visit. In Step 4, participants will receive injectable CAB LA + RPV LA first and second injections four weeks apart with subsequent injections every eight weeks through and including Week 96.

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

2.2 Hypotheses

Cohort 1: CAB (oral and LA) and RPV LA will be safe and will achieve pharmacokinetic targets through Week 16 in HIV-infected adolescents at the chosen dose to ultimately allow for a final dose to be selected.

Cohort 2: CAB LA and RPV LA, when given as dual therapy to stable, virologically suppressed adolescents will maintain viral suppression and will be safe through Week 24 in HIV-infected adolescents at the selected dose.

2.3 Study Objectives and Outcome Measures

2.3.1 Primary Objectives and Outcome Measures

Primary Objectives: Cohort 1 (continuing a background cART regimen)

- To confirm the doses for oral CAB followed by injectable CAB LA in HIV-infected, virologically suppressed adolescents by evaluating:
  - Safety and multiple dose PK of oral CAB through Week 4
  - Safety and multiple dose PK of CAB LA through Week 16
- To confirm doses for injectable RPV LA in HIV-infected, virologically suppressed adolescents by evaluating safety and multiple dose PK of RPV LA through Week 16

Outcome Measures

- Safety Outcome: All adverse events, regardless of grade
- Number of participants who:
  - Had Grade 3 or higher adverse events
  - Had Grade 3 or higher adverse events assessed as related to study product/s
  - Had serious adverse events meeting ICH criteria assessed as related to study product/s
  - Permanently discontinued study product due to adverse events assessed as related to study product/s
  - Died due to adverse events assessed as related to study product/s

- PK Outcome measures will be included in the PK Analysis Plan.

Primary Objective: Cohort 2 (discontinuing a background cART regimen)

• To assess the safety of CAB LA + RPV LA through Week 24 in HIV-infected, virologically suppressed adolescents

Outcome Measures

- Safety Outcome: All adverse events, regardless of grade
- Number of participants who:
  - Had Grade 3 or higher adverse events
  - Had Grade 3 or higher adverse events assessed as related to study product/s
  - Had serious adverse events meeting ICH criteria assessed as related to study product/s
  - Permanently discontinued study product due to adverse events assessed as related to study product/s
  - Died due to adverse events assessed as related to study product/s

2.3.2 Secondary Objectives and Outcome Measures

Secondary Objectives: Cohort 1

Secondary Objective 1:

- To monitor maintenance of viral suppression through Week 16 in HIV-infected, virologically suppressed adolescents

Outcome Measures

- Outcome: HIV-1 RNA through Week 16 for Cohort 1
- Number of participants with HIV-1 RNA < 50 copies/mL

Secondary Objectives 2 and 3:

- To evaluate the tolerability and acceptability of CAB LA through Week 16 in HIV-infected, virologically suppressed adolescents
- To evaluate the tolerability and acceptability of RPV LA through Week 16 in HIV-infected, virologically suppressed adolescents

Outcome Measures

- Tolerability measures will include measures of side effects, pain during and after injections, injection site reactions, and perceptions of injections from comprehensive surveys of adolescents
- Acceptability measures will include assessments of motivation for changing regimens, satisfaction with treatment, preferences for injectable versus oral regimen, quality of life, changes in attitudes towards the study products from comprehensive surveys of adolescents

Secondary Objectives: Cohort 2

Secondary Objective 4:

- To assess safety of oral CAB + oral RPV followed by CAB LA + RPV LA through Week 48 in HIV-infected, virologically suppressed adolescents

Outcome Measures

- Safety Outcome: All adverse events, regardless of grade
- Number of participants who:
  - Had Grade 3 or higher adverse events
  - Had Grade 3 or higher adverse events assessed as related to study product/s
  - Had serious adverse events meeting ICH criteria assessed as related to study product/s
  - Permanently discontinued study product due to adverse events assessed as related to study product/s
  - Died due to adverse events assessed as related to study product/s

Secondary Objective 5:

- To evaluate repeat-dose pharmacokinetics of CAB LA + RPV LA through Week 24, and through Week 48 in HIV-infected, virologically suppressed adolescents

Outcome Measures

Will be included in the PK Analysis Plan.

Secondary Objective 6:

- To assess antiviral activity of CAB LA + RPV LA through Week 24, and through Week 48 in HIV-infected, virologically suppressed adolescents

Outcome Measures

- Outcome: Plasma HIV-1 RNA
- Number of participants with HIV-1 RNA ≥50 copies/mL, HIV-1 RNA ≥200 copies/mL, per snapshot algorithm

3. Definitions

3.1 Baseline

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.

3.2 Analysis Populations

The following analysis populations are defined:

All Treated Population: All participants who took at least one dose of any study product.

Evaluable Population: For analysis purposes, evaluable participants will be defined as having been treated exclusively on the final recommended dose for a given cohort and either (1) having completed all treatment regimen through the said week periods (Week 4 or Week 16 for Cohort 1, Week 24 for Cohort 2), or (2) having experienced any of the following:

- death that is attributable to the study product/s, OR
- study product-related Grade 3+ events (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 without a prior period of exposure to one or the other; 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, even if they were out of window, the subject will be considered evaluable.

Cohort 2 Participants with Cohort 1 Experience: Cohort 2 participants who were previously enrolled to Cohort 1.

Cohort 2 Participants without Cohort 1 Experience: Cohort 2 participants who were enrolled directly to Cohort 2 without prior participation in Cohort 1.

4. Statistical Methods

4.1 General Considerations

For all baseline demographics and exposure analyses, results will be presented for All Treated Population.

Primary Analysis Reports for both Cohort 1 and Cohort 2 include analyses of both primary and secondary outcome measures only for evaluable participants ("Evaluable Population" as defined above). An additional requirement for inclusion in the primary analyses for Cohort 2 is that the participants must be directly accrued to Cohort 2 without prior exposure to one or the other study treatment drug ("**Cohort 2 Participants without Cohort 1 Experience**" as defined above).

In the Primary Analysis Reports, the appendix will include secondary analyses of safety and virologic analyses which will include all participants who received study product/s ("**All Treated Population**" referenced above).

All safety data will be considered from the first patient exposure to study treatment.

Note that additional analyses assessing the impact of COVID will be performed and the details will be included in the AIP.

4.2 Analyses

4.2.1 Primary Safety Analyses (Cohort 1 and Cohort 2)

The primary safety analyses will focus on the period from the start of study drug through Week 4 (CAB), and through Week 16 (CAB LA or RPV LA) for Cohort 1 and through Week 24 (oral CAB and oral RPV followed by CAB LA+RPV LA) for Cohort 2, where the primary safety analysis will include only evaluable participants. As an additional requirement, the safety analyses for Cohort 2 will only include **Cohort 2 Participants without Cohort 1 Experience** as defined above, which will be approximately 70 participants.

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 has completed 24 weeks on therapy.

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.

Proportions, bounded by exact 95% confidence intervals, will present participants experiencing:

(1) ≥ Grade 3 AEs,
(2) ≥ Grade 3 events which have been judged to be related to study product/s,
(3) serious adverse events meeting ICH criteria assessed as related to study product/s,
(4) permanent discontinuation of study product due to adverse events assessed as related to study product/s, and
(5) deaths due to product-related adverse events.

Overall proportions of participants meeting any of these criteria will be presented, in addition to specific proportions meeting each individual criterion.

Listings of all ≥ Grade 3 events regardless of treatment attribution, ≥Grade 3 events and serious adverse events meeting ICH criteria assessed as related to study product/s, as well as AEs which resulted in permanent discontinuation of study product/s or deaths will be provided, and will also be summarized and broken down by System Organ Class.

The proportions of participants meeting each of the endpoints which would trigger an SMC review will also be presented descriptively.

All proportions will be presented together with their 95% confidence intervals.

For regulatory submission purposes, all the above analyses will be performed for all Cohort 1 and Cohort 2 **Evaluable Population** and **All Treated Population**, separately. For Cohort 2, frequency distributions of the safety outcomes will be presented in aggregate and will be broken down by prior participation in Cohort 1 vs. exclusive participation in Cohort 2. In addition, the safety data will be presented separately for those who were enrolled under Version 2.0 and enrolled under Version 3.0.

Outcome Measures:

- All adverse events, regardless of grade
- Number of participants who:
  - Had Grade 3 or higher adverse events
  - Had Grade 3 or higher adverse events assessed as related to study product/s
  - Had serious adverse events meeting ICH criteria assessed as related to study product/s
  - Permanently discontinued study product due to adverse events assessed as related to study product/s
  - Died due to adverse events assessed as related to study product/s

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.

4.2.2 Secondary Analyses

Maintenance of Viral Suppression (Cohort 1)
Virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed through Week 16 for Cohort 1 participants. The proportion of participants maintaining suppression (<50 copies/mL) will be presented, along with the Exact 95% confidence intervals.

Outcome Measures:

- HIV-1 RNA through Week 16 for Cohort 1
- Number of participants with HIV-1 RNA < 50 copies/mL

Acceptability and Tolerability (Cohort 1)
Acceptability and tolerability measures on CAB LA or RPV LA reported by the Cohort 1 participants through Week 16 will be summarized using descriptive statistics**.**

Outcome Measures:

- Tolerability measures will include measures of side effects, pain during and after injections, injection site reactions, and perceptions of injections from comprehensive surveys of adolescents

- Acceptability measures will include assessments of motivation for changing regimens, satisfaction with treatment, preferences for injectable versus oral regimen, quality of life, changes in attitudes towards the study products from comprehensive surveys of adolescents

Safety Analyses (Cohort 2)
Week 24 (for Cohort 2) analyses described above for the primary analysis will be repeated as secondary analyses through Week 48 for the same participants mentioned under the primary analysis.

Outcome Measures:

- All adverse events, regardless of grade
- Number of participants who:
  - Had Grade 3 or higher adverse events

- Had Grade 3 or higher adverse events assessed as related to study product/s
- Had serious adverse events meeting ICH criteria assessed as related to study product/s
- Permanently discontinued study product due to adverse events assessed as related to study product/s
- Died due to adverse events assessed as related to study product/s

Note for Cohort 1 and Cohort 2: In addition to the primary analyses restricting the sample to appropriate participants as described above, further analyses which include safety data from **All Treated Population** through all mentioned periods will be performed. These secondary safety analyses will cover all safety data collected from first patient exposure to the study treatment to the end of the study. The Cohort 2 secondary analyses will include all participants whose treatment started in Cohort 1 at the final recommended dose and who progressed to Cohort 2 after completing participation in Cohort 1.

Descriptive and exposure-related analyses will present safety data from participants who were treated on doses other than the final recommended dose for their cohorts. This will include data representing the final dose for each cohort, as well as data gathered during the dose finding stage, which may represent exposure to doses which have failed. For each starting dose, every AE of ≥ Grade 3 will be listed, along with participant demographics, the dose prescribed to the patient at the time of the event and the protocol team's assessment whether this event was due to the study products.

Virologic Activity (Cohort 2)

Virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed at Weeks 24 and 48 for evaluable Cohort 2 participants. At both of these time points the virologic outcome will be calculated according to the FDA's snapshot algorithm with three main categories (i.e. HIV-1 RNA<50 copies/mL, HIV-1 RNA≥50 copies/mL, and no virologic data). Full details of the Snapshot algorithm are in the Appendix. The snapshot outcome will be presented at both Week 24 and Week 48. The Exact 95% confidence intervals for the proportion of participants with HIV-1 RNA<50 c/mL will be calculated. The similar summary and analysis will also be performed using the cutoff of HIV-1 RNA 200 copies/mL. In addition to the snapshot analysis, the proportions of participants meeting the criteria for confirmed virologic failure through Week 24 and Week 48 will also be presented.

In addition, the above analyses results will also be presented for **all treated** Cohort 2 participants ("**All Treated Population**" as defined above).

Outcome Measures:

- Plasma HIV-1 RNA
- Number of participants with HIV-1 RNA >200 copies/mL, missing HIV-1 RNA, study treatment discontinuations

Note: Secondary outcome measure (Virologic Activity through Week 24) will be evaluated concurrently with the primary outcome measures; additional longer-term secondary objectives will be evaluated as outcome measures become available and will be posted to ClinicalTrials.Gov. The final updating of the AE tables will be done once the last participant enrolled in Cohort 2 has completed 48 weeks of long-term safety and washout PK follow-up (LSFU) [i.e., after reaching Week 144].

5. Core Manuscript Writing Team

6. Protocol History

Protocol Version 1
Version 1.0, dated March 2, 2018, however this version was never implemented.

Protocol Version 2
Version 2.0, dated 16 August 2020, was implemented at sites with the first enrollment occurring on April 3, 2019. Accrual was paused on 17 March 2020 due to the COVID-19 pandemic.

Protocol Version 3
Version 3.0, dated 13 August 2020, was finalized and distributed to sites on August 18, 2020.

7. Appendix

7.1 Snapshot Approach – Detailed Algorithm Steps (using Cutoff of HIV-1 RNA 200 c/mL as an Example)

Condition ('Week 24' indicates Week 24 window)	**Response**	**Reasons**
1. If ***non-permitted*** change in background therapy ***prior to*** Week 24	HIV1-RNA ≥ 200	Change in ART
2. If ***permitted*** change in background therapy ***prior to*** Week 24 AND the latest on-treatment VL prior to/on the date of change is ≥ 200 c/m	HIV1-RNA ≥ 200	Change in ART
3: If ***non-permitted*** change in background therapy ***during*** Week 24		
• Last on-treatment VL during Week 24 prior to/on the date of change ≥ 200 c/mL	HIV1-RNA ≥ 200	Data in window and HIV-1 RNA >= 200 copies/mL
• Last on-treatment VL during Week 24 prior to/on the date of change <200 c/mL	HIV1-RNA < 200	
• No VL during Week 24 prior to/on the date of change	HIV1-RNA ≥ 200	Change in ART
4: If ***permitted*** change in background therapy ***during*** Week 24 AND the last on-treatment VL prior to/on the date of change is ≥ 200 c/mL		
4.1 this last on-treatment VL occurs prior to Week 24	HIV1-RNA ≥ 200	Change in ART
4. 2 this last on-treatment VL occurs during Week 24 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		
• Last on-treatment VL during Week 24 ≥ 200 c/mL	HIV1-RNA ≥ 200	Data in window and HIV-1 RNA >= 200 copies/mL
• Last on-treatment VL during Week 24 <200 c/mL	HIV1-RNA < 200	

Condition ('Week 24' indicates Week 24 window)	**Response**	**Reasons**
5.2 No VL during Week 24		
i. 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
ii. If subjects withdraw before/during Week 24 due to		
1. 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
2. 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)		
• 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
• Last on-treatment VL ≥ 200 c/mL AND withdrawal due to Lack of efficacy	HIV1-RNA ≥ 200	Disc. for lack of efficacy
• 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:
    a. 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.
    b. 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.*

Optimized Background Therapy Substitutions After Randomization (not relevant to this study as there is no OBT in this study)

- OBT substitutions (in-class or cross-class) permitted per protocol for documented toxicity reasons can be permitted on or before the first trial visit without penalty.

If OBT substitutions for toxicity reasons occur after the first trial visit, then patients should be categorized as having HIV-RNA greater than or equal to 50 copies/mL if they have HIV-RNA above 50 copies/mL at the time of switch.