IMPAACT 2017

IND #: 138,754 Held By DAIDS
DAIDS ID #30070

This file contains the current IMPAACT 2017 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #1, dated 20 May 2020
- Clarification Memorandum #2, dated 31 March 2020
- Clarification Memorandum #1, dated 22 January 2019
- Protocol Version 2.0, dated 16 August 2018
Letter of Amendment #1 for:

IMPAACT 2017

“MOCHA”

More Options for Children and Adolescents

Version 2.0, dated 16 August 2018

DAIDS Study ID #30070
IND #138,754

Letter of Amendment Date: 20 May 2020

Table of Contents

Information/Instructions to Study Sites from the Division of AIDS .......................................................... 1
Letter of Amendment Signature Page............................................................................................................. 2
Summary of Modifications and Rationale .................................................................................................... 3
  A. Protocol Team Roster Updates .............................................................................................................. 3
  B. Decrease in the target samples sizes for the Cohort 1 interim analysis ............................................... 5
  C. Operational Guidance from Protocol CM #2, dated 31 March 2020................................................... 9

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2017 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All applicable IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT 2017. If the IMPAACT 2017 protocol is amended in the future, applicable contents of this LoA will be incorporated into the next version of the protocol.
I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

__________
Signature of Investigator of Record

__________
Date

__________
Name of Investigator of Record
(printed)
Summary of Modifications and Rationale

The purpose of this LoA is to update the protocol team roster to reflect current membership, decrease the target sample sizes for the Cohort 1 interim analysis in the protocol, and incorporate the contents of protocol Clarification Memorandum (CM) #2.

Section A of this LoA includes the protocol team roster updates and some of the contents of CM #1, dated 22 January 2019.

Section B of this LoA includes modifications associated with decreasing the target sample size for the Cohort 1 interim analysis. The sample size will be decreased slightly from a target of eight in each of Cohorts 1C and 1R to a target of seven in each cohort. Preliminary study data support this change, as the PK model established prior to the study has been strongly predictive, data collected in the study to date for adolescents have been consistent with data previously collected for adults, and no safety concerns have been identified.

Section C of this LoA incorporates the contents of CM #2, which was issued on 31 March 2020 to safeguard the health and well-being of study participants in the context of circulating SARS-CoV-2 and the associated COVID-19 pandemic. CM #2 provided operational flexibility for conducting study visits and procedures when needed to ensure ongoing access to study drug and to prioritize the conduct of clinically and scientifically important laboratory evaluations when possible. Per the study Sponsor, sites were instructed to implement the guidance provided in CM #2 immediately. All sites should continue to follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures during the COVID-19 pandemic, with utmost importance placed on the health and well-being of study participants and study staff. Consistent with the instructions provided in CM #2, implementation of Section C of this LoA is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT 2017 Protocol Team will determine when, in the future, the guidance in Section C is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform IRBs/ECs and other applicable regulatory entities.

Implementation

Modifications of protocol text are shown in Sections A and B of this LoA, using strikethrough for deletions and bold type for additions where appropriate. Within these sections, modifications are generally shown in order of appearance in the protocol. Operational guidance for conducting study visits and procedures during the COVID-19 pandemic is provided in Section C of this LoA; conventions for use of strikethrough and bolding do not apply in this section.

A. Protocol Team Roster Updates

To reflect current protocol team membership, Emily Brown, Rohan Hazra, Terence Fenton, Parul Patel, Susan Ford, Peter Williams, and Carolyn Yanavich are removed from the protocol team roster (deletion not shown). Bill Kapogiannis, Michelle Hsu, Allison Agwu, Conn Harrington, Mark Baker, Navin Goyal, Jenny Huang, Kati Vandermeulen, and Katie Trabert are added; Bill Kapogiannis is also added as the NICHD Medical Officer on the protocol cover page. Other modifications are shown below.
Protocol Laboratory Data Managers
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B. Decrease in the target samples sizes for the Cohort 1 interim analysis

1. Protocol Section 1.3.1, Study Monitoring Committee Review, newly added sub-section is shown below, other sub-sections will be re-numbered accordingly (not shown):

Preliminary PK data were reviewed by the Study Monitoring Committee on Jan 17, 2020 and were found to achieve PK targets.

At the time of the January 2020 SMC review, a total of 16 participants had PK collected and analyzed, 7 in Cohort 1C (CAB) and 9 in Cohort 1R (RPV). The Cohort 1C median PK parameters were within the desired median target median PK ranges, at Week 2 PO (n=7) and Week 16 IM (n=4) - PO AUC observed median (target range): 167.4 (131.1-326.8) mcg*h/mL and IM trough: 3.1 (1.2-6.2) mcg/mL. Similarly, the median Cohort 1R PK parameter was within the desired median PK target range at Week 16 IM troughs (n=6) - observed median (target range): 43.8 (40.7-126) ng/mL.

Adult CAB and RPV LA POP PK models developed using PK data from adult clinical studies were used to predict the expected CAB and RPV PK from adolescents in IMPAACT 2017. Simulations were conducted with these models, modified to include expected age and weight related impact on adolescent PK, and used to determine expected exposure in adolescents using the standard adult efficacious Q4W dosage. The preliminary adolescent PK data from the SMC review were compared against these a priori model predictions. The observed concentrations are centered around the predicted median and predominantly within the 90% prediction intervals as displayed in Figures 7 and 8 for CAB and RPV respectively.
Figure 7: Observed preliminary IMPAACT 2017 Cohort 1C CAB concentrations in adolescents compared to model predicted concentrations based on POP PK analyses from adult studies

Note: The plots represent the CAB systemic exposure: solid line and shaded band reflect the population pharmacokinetic model predictions (median and 90% interval); the dots represent the observed individual subject data. The dashed lines represent the maximum observed geometric mean exposure from the TQT study at (22.5 mcg/mL) at supratherapeutic doses following 150 mg q12h x 3 and the target threshold concentrations at trough (0.65 mcg/mL).
Figure 8a: Observed IMPAACT 2017 Cohort 1R preliminary data and predicted RPV plasma concentrations in adolescents after PO RPV 25 mg once daily (left panel) and IM RPV LA 900-600-600 mg (right panel)

Note: Black line and blue shaded area: median and 90% prediction interval for adolescents; black dots: observed data in Cohort 1R adolescents

Figure 8b: Observed trough RPV plasma concentrations in Cohort 1R adolescents (blue dots) and adults (boxplots, ATLAS/FLAIR) after PO RPV 25 mg once daily (Week 0; last day of PO lead-in), and IM RPV LA 900-600-600 mg (Weeks 4, 8 and 12; concentrations 4 weeks after injection)

The agreement of the preliminary observed PK data with the expected criteria and model simulations indicated that the respective POP PK models for CAB and RPV are capable of accurately predicting PK in adolescents with no unexpected PK issue. Additionally, adolescent PK is generally expected to vary only slightly from adult PK for most drugs and it is commonplace to use adult dose regimes for adolescents. Of 92 products assessed by the FDA, 95% had equivalent dosing for adults and adolescent patients (17a). When give the same CAB
and RPV dosage as adults, slightly higher mean exposures are expected in adolescents due to their lower body weights. These differences are however not likely to be clinically relevant given the broad range of exposures observed in adults.

The observed concentrations following PO and IM administration are well predicted by the POP PK models with nearly all the individual participants values within the 90% prediction intervals throughout the PK sampling interval. This dosing provides exposures comparable to those previously seen adults and it is highly unlikely that collection of additional PK data with the current dosing regimen would impact conclusions about exposure adequacy for CAB or RPV.

Preliminary safety data was reviewed by the SMC in March 2020, and no safety issues or concerns were identified. All available safety data for the eight participants in Cohort 1C and 15 participants in Cohort 1R were presented. At the time of the review, based on the available data, the following were deemed evaluable (with PK and Week 16 safety data): seven evaluable participants in Cohort 1C, and nine evaluable participants in Cohort 1R.

The safety data used in the March 2020 review showed that out of the seven evaluable participants in Cohort 1C, only one participant had a Grade 3 study product-related AE but remained in the study. Of the first 8 evaluable participants in Cohort 1R, only one participant had a Grade 3 study product-related AE which resulted in permanent discontinuation of study treatment. There were no safety concerns for the other participants in both cohorts.

For Cohort 1R, all 8 evaluable participants had already passed the safety guidelines in Section 9.5.1.3 of protocol Version 2.0. For Cohort 1C, the current available data confirm that the 8th evaluable participant in this cohort has no safety concerns.

2. All references to the revised interim analysis target sample size have been revised from 8 to 7 evaluable participants for Cohort 1C and Cohort 1R as shown below in Section 3.0. The following will also be affected by this revision: Figure 1 in the Schema, Sections 1.3.2, 1.3.3, 3.1, 9.5.1, 9.5.2, 10.2, and 10.4.1 (changes not shown).

An interim analysis of safety and PK data will be performed (as described in Sections 9 and 10) following the first eight seven evaluable Cohort 1C and the first eight seven evaluable Cohort 1R participants completing their Cohort 1, Step 2 Week 16 study visit.

3. Protocol Section 9.5.1, Monitoring by the Protocol Team, Safety Guidelines for the First 87 Evaluable Participants Started at a Given Dose Level in Each Group in Cohort 1, eighth and ninth paragraphs and Table 10:

As an example of how to read Table 10, the second row shows that there is a 93% 87% chance of failing the safety guidelines at doses in which the true rate of study product-related life-threatening AEs is 5% and the true rate of study product-related non-life-threatening adverse events is 50%.

| Table 1. Probability of Failing Dose Guidelines Under Potential Rates of True Toxicity |
|---------------------------------|---------------------------------|-----------------|
| True Toxicity Rates             | Probability of Failing          |
| Non-life threatening study       | Safety Guidelines               |
| product-related Grade 3+ AEs,   |                                 |
| 0.50                            | 0.860.77                        |
| Study product related life-     |                                 |
| threatening Grade 4 AEs         |                                 |
| 0.00                            |                                 |
Under the conditions specified in row 2 of the table, assuming that it would be undesirable to treat additional subjects at a dose that had these true rates of adverse events, the 7% 13% chance of NOT failing the safety guidelines would represent the probability of error. As a further example, the table also shows that there is 4% 0.4% chance of failing, when the true rate of study product-related non-life-threatening AE is only 5% and the true rate of study product-related life-threatening AE is zero. Assuming that the potential benefits associated with exposing additional subjects to this dose of the study product would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

4. The following reference was added in Section 17, References:


**C. Operational Guidance from Protocol CM #2, dated 31 March 2020**

This CM provides operational guidance to study sites from the IMPAACT 2017 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff. Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the Clinical Management Committee (impaact.2017cmc@fstrf.org) with any questions or concerns regarding this CM or management of study participants.
Visit Scheduling

- Sites that anticipate operational disruptions or closures in the near future are advised to conduct study visits early in the allowable visit window.
- Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the allowable visit window.

Prioritization of Study Visit Procedures

- Adherence counseling regarding the importance of maintaining background cART regimens should be conducted for all study participants at each study visit, until further notice.
- Before any PK specimen is collected, sites should verify that they are able to store PK samples locally and under the specifications described in the Laboratory Processing Chart (LPC). In addition to storing PK samples locally, all sites must store plasma samples for genotypic and phenotypic resistance testing locally and under the specifications described in the LPC until further notice.
- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Study product injections may not be administered outside of the clinical research site. Sites should carefully assess their ability to monitor safety of participants on study. Only when safety monitoring can be adequately assured for the participant’s study visits should sites consider administering the injectable study drug. Additionally, study product injections should only be administered at the site when collection and appropriate storage of PK samples is possible. Study procedures listed in protocol Section 6.9 must be conducted prior to any administration of study product.
- For sites unable to administer study product injections at the clinical research site: Cohort 1 Step 2 participants with study product injections remaining (i.e., Week 8 or Week 12 study visits yet to be completed) should be permanently discontinued from injectable study product and followed per the long-term safety and washout PK follow-up (LSFU) visit schedule.
- If health authority, IRB/ECs, government, institutional and local policies allow, sites with limited capacity to conduct in-person clinic visits may also conduct study visits — in full or in part — off-site or virtually (via telephone or other appropriate method), noting study product injections must be administered at the clinical research site. Where off-site or virtual study visits are permitted, site staff should communicate with participants (and parent/legal guardian as applicable) to determine in advance visit details with adequate protections for safety, privacy, and confidentiality. Off-site and virtual visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site or virtual visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.
- Sites with limited capacity to conduct study visits (whether in-person or virtually) should prioritize the following procedures:
  - Adherence counseling to maintain the participant’s ongoing background cART regimen; this may be conducted virtually.
  - Clinical procedures/evaluations; local institutional guidance may be followed for prioritization of clinical procedures and evaluations and guided by participant safety. Medical and medication histories may be obtained virtually.
  - Laboratory procedures and evaluations (see protocol Section 6.16.1 for specimen prioritization).
  - Contraceptive counseling may be conducted virtually.
  - Acceptability/tolerability questionnaires may be administered virtually or skipped/missed.
**Documentation**

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2017.
- Documentation should be entered in participant study charts in real-time should any of the following occur:
  - Missed visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed, and which were not)
  - Virtual visit/remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
- In consultation with DAIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.
Clarification Memorandum #2 for:

IMPAACT 2017

“MOCHA”

More Options for Children and Adolescents

Version 2.0, dated 16 August 2018

DAIDS ID #30070
IND #138,754 Held by DAIDS

Clarification Memorandum Date: 31 March 2020

Summary of Clarifications and Rationale

This Clarification Memorandum (CM) is being issued to safeguard the health and well-being of IMPAACT 2017 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic.

As the study Sponsor, the Division of AIDS (DAIDS) has determined that this CM should be implemented immediately upon issuance. Consistent with the United States Food and Drug Administration guidance, Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by DAIDS prior to implementation. However, given the context of the COVID-19 pandemic and the importance of the guidance provided in this CM, sites should submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their review and approval.

The purpose of this CM is to provide operational flexibility for conducting study visits and procedures when needed to ensure monitoring participant safety and to prioritize the conduct of clinically and scientifically important evaluations when possible.

Implementation of this CM is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT 2017 Protocol Team will determine when, in the future, the guidance provided in this CM is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform their IRBs/ECs.

Please file this CM and any applicable IRB/EC correspondence in your essential document files for IMPAACT 2017.
Implementation

This CM provides operational guidance to study sites from the IMPAACT 2017 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the Clinical Management Committee (impaaact.2017cmc@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

Visit Scheduling

- Sites that anticipate operational disruptions or closures in the near future are advised to conduct study visits early in the allowable visit window.
- Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the allowable visit window.

Prioritization of Study Visit Procedures

- Adherence counseling regarding the importance of maintaining background cART regimens should be conducted for all study participants at each study visit, until further notice.
- Before any PK specimen is collected, sites should verify that they are able to store PK samples locally and under the specifications described in the Laboratory Processing Chart (LPC). In addition to storing PK samples locally, all sites must store plasma samples for genotypic and phenotypic resistance testing locally and under the specifications described in the LPC until further notice.
- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Study product injections may not be administered outside of the clinical research site. Sites should carefully assess their ability to monitor safety of participants on study. Only when safety monitoring can be adequately assured for the participant’s study visits should sites consider administering the injectable study drug. Additionally, study product injections should only be administered at the site when collection and appropriate storage of PK samples is possible. Study procedures listed in protocol Section 6.9 must be conducted prior to any administration of study product.
- For sites unable to administer study product injections at the clinical research site: Cohort 1 Step 2 participants with study product injections remaining (i.e., Week 8 or Week 12 study visits yet to be completed) should be permanently discontinued from injectable study product and followed per the long-term safety and washout PK follow-up (LSFU) visit schedule.
- If health authority, IRB/ECs, government, institutional and local policies allow, sites with limited capacity to conduct in-person clinic visits may also conduct study visits — in full or in part — off-site or virtually (via telephone or other appropriate method), noting study product injections must be administered at the clinical research site. Where off-site or virtual study visits are permitted, site staff should communicate with participants (and parent/legal guardian as applicable) to determine in advance visit details with adequate protections for safety, privacy, and confidentiality. Off-site and virtual visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site or virtual visit, staff conducting the visit...
should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.

- Sites with limited capacity to conduct study visits (whether in-person or virtually) should prioritize the following procedures:
  - Adherence counseling to maintain the participant’s ongoing background cART regimen; this may be conducted virtually.
  - Clinical procedures/evaluations; local institutional guidance may be followed for prioritization of clinical procedures and evaluations and guided by participant safety. Medical and medication histories may be obtained virtually.
  - Laboratory procedures and evaluations (see protocol Section 6.16.1 for specimen prioritization).
  - Contraceptive counseling may be conducted virtually.
  - Acceptability/tolerability questionnaires may be administered virtually or skipped/missed.

**Documentation**

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2017.
- Documentation should be entered in participant study charts in real-time should any of the following occur:
  - Missed visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed, and which were not)
  - Virtual visit/remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
- In consultation with DAIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.
Clarification Memorandum # 1 for:

IMPAACT 2017

“MOCHA”
More Options for Children and Adolescents
Version 2.0, dated 16 August 2018

DAIDS ID # 30070
IND # 138,754 Held By DAIDS

Clarification Memorandum Date: 22 January 2019

Summary of Clarifications and Rationale
This Clarification Memorandum (CM) clarifies portions of the Schedules of Evaluations for consistency with protocol text regarding total maximum blood draw volumes, pharmacokinetic (PK) blood draw volumes, and pregnancy testing. This CM also clarifies the use of the term “sex at birth” in specified sections, such as describing the demographics which will be used for the PK analysis, as participant “gender” is neither intended nor collected as study data. This CM also updates the protocol team roster and references to DAIDS Regulatory Support Center (RSC) websites.

Implementation
This CM has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation. However, sites may submit this CM to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The content of the CM does not impact the sample informed consent forms for the study or the benefit-to-risk ratio for study participants. The sample informed consent forms permit collection of required blood draw volumes as clarified in this CM.

This CM should be maintained in each site’s essential documents file for IMPAACT 2017. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT 2017 protocol.

The clarifications and updates included in this CM are listed below in order of appearance within a specified clarification in the protocol. Additions to the text are indicated in bold; deletions are indicated by strike-through.
1. Protocol Team Roster Updates
To reflect current team membership, the following persons are removed from the roster Edward Acosta, Viviam Canon, Korianne Sulzbach, William A. Murtaugh, and Bill Kabat; the persons listed below are added to the roster.

Clinical Trials Specialists:
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2. Referenced Website Updates
References to the DAIDS RSC websites are updated as shown in items a-c.

a) Section 7.3.1, EAE Reporting to DAIDS, Page 106, 1st and 2nd paragraphs:
http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual

b) Section 7.3.3, Grading Severity of Events (applies to EAEs and all other adverse events), Page 107, 1st paragraph, last sentence:
http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables
https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

c) Section 15.2, Protocol Registration, Page 156, 4th paragraph, last sentence:
http://rsc.tech-res.com/protocolregistration/
https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration

3. Clarifies the term sex (rather than gender)
The term “gender” is replaced with the term “sex at birth” as shown in items a-c.

a) Section 9.4, Sample Size and Accrual, Page 125, 1st paragraph, 1st sentence:
The term gender is replaced with the term sex to describe the sample size stratification which is based on sex at birth, as follows:

The sample size is the minimum number of participants, agreed upon by the industry sponsor and regulators and driven primarily by safety considerations, which is likely to be needed to determine the dosage across the possible weight, age and gender sex at birth distributions.

b) Section 10.2, Primary and Secondary Data Cohorts 1 and 2, Page 140, 1st paragraph, 1st sentence:
The term gender is replaced with the term sex to describe the demographics which will be used in the PK analysis, as follows:

Demographic data used in the PK analysis will include age, gender sex at birth, race, ethnicity, height, weight, weight Z score, weight group (35-<50kg vs ≥50kg), BMI, and BSI.

c) Section 11.1, Sample Size and Selection Process, Page 146, 2nd paragraph, 1st sentence:
The term gender is replaced with the term sex to describe the sample size stratification which is based on sex at birth, as follows:

Self-reported demographics from Screening and Entry visits will be used to inform selection with the goal of balancing participant gender sex at birth and age (both older and younger adolescents) in the completed interviews.

4. Schedule of Evaluations (SoE) Clarifications
The SoEs for Cohorts 1 and 2, and Long-Term Safety and Washout PK Follow-Up visits are clarified as shown in items a-e.

a) **Appendix I-A, Schedule of Evaluations for Cohort 1 Adolescents (Cohort 1C and Cohort 1R), Page 160, Row Total Maximum blood volume, Column CT 1 Wk 16**: The total maximum blood draw volume for the Cohort 1 Week 16 visit was miscalculated as is corrected as follows:

21 mL, 22 mL

b) **Appendix I-B, Schedule of Evaluations for Cohort 2 Adolescents, Page 163, Row Total Maximum blood volume, Column CT 2 Wk 8, 12, 16, 20, 24**: The minimum total required blood volume was not specified for the Cohort 2 Week 8, 12, 16, and 20 visits and is added as follows:

21-24 mL

c) **Appendix I-C, Schedule of Evaluations for Long-Term Safety and Washout PK Follow-Up (LSFU) Adolescents, Page 164, Row PK Sampling, Column LSFU Week 48/Early Termination**: The minimum PK sampling blood draw volume was not specified for the LSFU Week 48/Early Termination visit and the associated footnotes were incorrectly referenced; these issues are addressed as follows:

20-4 mL

4-7

d) **Appendix I-C, Schedule of Evaluations for Long-Term Safety and Washout PK Follow-Up (LSFU) Adolescents, Page 164, Row PK Sampling, Column Confirmation of Virologic Failure**: The footnote associated with PK Sampling was incorrectly referenced and is corrected as follows:

2-4 mL

4-7

e) **Appendix I-C, Schedule of Evaluations for Long-Term Safety and Washout PK Follow-Up (LSFU) Adolescents, Page 164, Row hCG (females only), Column Confirmation of Virologic Failure**: Pregnancy testing was inadvertently not indicated as a required procedure at the Confirmation of Virologic Failure visit and is corrected as follows:

<table>
<thead>
<tr>
<th>Confirmation of Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCG (females only)(^5)</td>
</tr>
</tbody>
</table>

“MOCHA”
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A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

Pharmaceutical Support Provided by:
ViiV Healthcare

DAIDS ID #30070
IND #138,754 Held By DAIDS

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TABLE OF CONTENTS

Protocol Signature Page ................................................................. 6
ABBREVIATIONS AND ACRONYMS .................................................... 7
PROTOCOL TEAM ROSTER ................................................................. 9
STUDY SITE ROSTER ......................................................................... 12
SCHEMA ......................................................................................... 16

1 INTRODUCTION ....................................................................... 23
  1.1 Background ............................................................................. 23
  1.2 Prior Research .......................................................................... 24
  1.3 Rationale .................................................................................. 36
  1.4 Risk/Benefit Assessment ............................................................. 44
  1.5 Hypotheses .............................................................................. 45

2 OBJECTIVES ........................................................................... 45
  2.1 Primary Objective: Cohort 1 (continuing a background cART regimen) . 45
  2.2 Primary Objective: Cohort 2 (discontinuing a background cART regimen) . 46
  2.3 Secondary Objectives: Cohort 1 .................................................. 46
  2.4 Secondary Objectives: Cohort 2 .................................................. 46
  2.5 Other Objectives ....................................................................... 46

3 STUDY DESIGN ....................................................................... 47
  3.1 Cohort 1 .................................................................................. 48
  3.2 Cohort 2 .................................................................................. 49
  3.3 Long-term Safety and Washout PK Follow-up (LSFU) ..................... 50

4 STUDY POPULATION ................................................................ 51
  4.1 Inclusion Criteria: Cohort 1 Step 1 and Cohort 2 Step 3 .................. 52
  4.2 Exclusion Criteria: Cohort 1 Step 1, or Cohort 2 Step 3 ................. 54
  4.3 Inclusion/Exclusion Criteria, Step 2 (Cohort 1 Progression Criteria, Step 1 to Step 2) . 55
  4.4 Inclusion/Exclusion Criteria, Step 4 (Cohort 2 Progression Criteria, Step 3 to Step 4) . 56
  4.5 Inclusion/Exclusion Criteria: Parents/Caregivers ......................... 57
  4.6 Co-Enrollment Considerations ................................................... 58
  4.7 Recruitment, Screening, and Enrollment Process ......................... 58
  4.8 Participant Retention .................................................................. 59

5 STUDY PRODUCT .................................................................... 60
  5.1 Study Product Regimen and Administration ............................... 60
  5.2 Study Product Formulation ......................................................... 63
  5.3 Study Product Supply ................................................................. 63
  5.4 Study Product Accountability ...................................................... 64
  5.5 Final Disposition of Study Product ............................................. 64
  5.6 Concomitant Medications ......................................................... 64
  5.7 Prohibited Medications .............................................................. 64
  5.8 Precautionary Medications ......................................................... 64

6 STUDY VISITS AND PROCEDURES ..................................... 65
  6.1 Study Visit Windows, Split and Interim Visits ............................ 65
  6.2 Cohort 1 Step 1, and Cohort 2 Step 3 Screening Visit ................. 67
  6.3 Cohort 1 .................................................................................. 68
LIST OF FIGURES

Figure 1. Overview of Study Design for Cohort 1 Participants .......................................................... 19
Figure 2. Overview of Study Design for Cohort 2 Participants .......................................................... 20
Figure 3. Overview of Study Participation Flow for Cohort 1 Participants ........................................ 21
Figure 4. Overview of Study Participation Flow for Cohort 2 Participants ........................................ 22
Figure 5. Proportion of patients with HIV-1 RNA concentration less than 50 copies per mL (FDA snapshot algorithm) by visit at week 96 in the LATTE-2 study ......................................................... 33
Figure 6. Injection Site Reactions (ISRs) for CAB LA or RPV LA over time through week 96 in the LATTE 2 study .................................................................................................................. 34
Figure 7. Summary of patient-reported outcomes at (A) week 48 (maintenance treatment) and (B) week 96 in the LATTE-2 study .......................................................................................................... 35
Figure 8. Simulated Steady State CAB Concentration-Time Profile over the Dosing Interval following 30mg Once Daily (35 to <50kg left panel, ≥ 50kg right panel) ....................................................... 40
Figure 9. Simulated CAB Concentration-Time Profile following CAB LA 600mg Dose 1 and 400mg IM Q4W (35 to <50kg left panel, ≥ 50kg right panel) ................................................................. 42

LIST OF TABLES

Table 1. Predicted Steady State CAB Parameters following Oral CAB 30mg QD in Adolescents compared to Observed Adult Values ........................................................................................................ 39
Table 2. Predicted Steady State CAB Parameters following CAB LA 400mg IM Q4W compared with Observed data in Adults ........................................................................................................... 41
Table 3. Predicted Steady State RPV PK Parameters following RPV LA 600mg IM Q4W compared with Predicted data for oral RPV and RPV LA Q4W in Adults ..................................................................... 43
Table 4. Comparison of Predicted Median (90% PI) Trough following 3rd IM dose given every 4 weeks versus at steady state in adolescents 35 kg and above ................................................................................. 43
Table 5. Cohort 1: Study Product Regimen and Administration ............................................................... 61
Table 6. Cohort 2: Study Product Regimen and Administration ............................................................... 61
Table 7. Documentation Requirements for Medical and Medication Histories ........................................ 97
Table 8. Visits Requiring Complete Physical Examination ................................................................. 98
Table 9. Percent of Participants Experiencing ≥ Grade 3 Adverse Events (or ≥ Grade 3 Adverse Events Attributed to the Study Medications) with Exact 95% Confidence Intervals .............................................. 126
Table 10. Probability of Failing Dose Guidelines Under Potential Rates of True Toxicity ...................... 130
Table 11. Probability of Failing Dose Guidelines Under Potential Rates of True Toxicity ..................... 132
Table 12. Percent of Participants Meeting Criterion for Virologic Success with Exact .......................... 137
IMPAACT 2017
DAIDS Study ID #30070

Version 2.0
Protocol Signature Page

I will conduct this study in accordance with the provisions of this protocol amendment and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Signature of Investigator of Record

Date

Name of Investigator of Record
(printed)
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ABBREVIATIONS AND ACRONYMS

AE  Adverse Event
AIDS  Acquired Immunodeficiency Syndrome
ALT  Alanine Transaminase
ARV  Antiretroviral
ART  Antiretroviral Therapy
AST  Aspartate Aminotransferase
AUC  Area under the plasma concentration-time curve
BMI  Body Mass Index
CAB  Cabotegravir
CAB LA  Long-Acting Injectable Cabotegravir
cART  Combination Antiretroviral Therapy
CBC  Complete Blood Count
CFR  Code of Federal Regulations
CL/F  Apparent total body clearance
Cmax  Maximum concentration
CMC  Clinical Management Committee
CPK  Creatine phosphokinase
CRMS  NIAID Clinical Research Management System
CRPMC  NIAID Clinical Research Products Management Center
CT  Cohort
Ct  Concentration at the end of the dose interval
CNDx  Concentration at a specified time (x) after administration of a specific dose number (ND)
CV%  Coefficient of variation
DAIDS  Division of AIDS
DAIDS RSC  DAIDS Regulatory Support Center
DAERS  DAIDS Adverse Experience Reporting System
DMC  Data Management Center
DTG  Dolutegravir
EAE  Expedited Adverse Event
EC  Ethics Committee
ECG/EKG  Electrocardiogram
eCRF  Electronic Case Report Form
EFV  Efavirenz
EU  European Union
FDA  Food and Drug Administration
FSTRF  Frontier Science and Technology Research Foundation
GCP  Good Clinical Practices
hCG  Human Chorionic Gonadotropin
HIV  Human Immunodeficiency Virus
HVTN  HIV Vaccine Trials Network
IATA  International Air Transport Association
IB  Investigator’s Brochure
ICH  International Conference on Harmonisation
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<td>IM</td>
<td>Intramuscular</td>
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<td>IMPAACT</td>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials Network</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>INSTI</td>
<td>Integrate Strand Transfer Inhibitor</td>
</tr>
<tr>
<td>IoR</td>
<td>Investigator of Record</td>
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<tr>
<td>IRB</td>
<td>Institutional review board</td>
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<tr>
<td>ISR</td>
<td>Injection site reaction</td>
</tr>
<tr>
<td>LA</td>
<td>Long-acting</td>
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<td>LPC</td>
<td>Laboratory processing chart</td>
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<td>Long-term Safety and Washout PK Follow-Up</td>
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<td>MOCHA</td>
<td>More Options for Children and Adolescents</td>
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<tr>
<td>MOP</td>
<td>Manual of Procedures</td>
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<td>National Institutes of Health</td>
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<tr>
<td>NIMH</td>
<td>National Institute of Mental Health</td>
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<tr>
<td>NNRTI</td>
<td>Non-nucleoside Reverse Transcriptase Inhibitor</td>
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<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitors</td>
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<tr>
<td>NTD</td>
<td>Neural Tube Defect</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
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<td>PID</td>
<td>Participant Identification Number</td>
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<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
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<tr>
<td>PO</td>
<td>By mouth</td>
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<tr>
<td>PoR</td>
<td>Pharmacist of Record</td>
</tr>
<tr>
<td>QTc</td>
<td>Corrected Q-T interval</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic Acid</td>
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<tr>
<td>RPV</td>
<td>Rilpivirine</td>
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<tr>
<td>RPV LA</td>
<td>Long-acting injectable rilpivirine</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
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<tr>
<td>SES</td>
<td>Subject Enrollment System</td>
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<td>SID</td>
<td>Study Identification Number</td>
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<tr>
<td>SMC</td>
<td>Study Monitoring Committee</td>
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<tr>
<td>SMR</td>
<td>Sexual Maturity Rating</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SUSAR</td>
<td>Suspected, Unexpected Serious Adverse Reactions</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>Time of maximum concentration</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
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<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>V/F</td>
<td>Apparent volume of distribution</td>
</tr>
</tbody>
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**SCHEMA**

**Purpose:** To confirm the dose and evaluate the safety, tolerability, acceptability, and pharmacokinetics (PK) of oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), and long-acting injectable rilpivirine (RPV LA) in virologically suppressed HIV-1 infected children and adolescents aged 12 to <18 years.

**Design:** Phase I/II, multi-centre, open-label, non-comparative study

**Study Population:** HIV-1 infected children and adolescents, 12 to <18 years of age, who are virologically suppressed on stable cART consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs, and selected parents/caregivers.

**Sample Size:** Up to 155 adolescents in total

**Cohort 1:** Up to 55 adolescents to achieve approximately 35 evaluable receiving the oral followed by the LA dose of CAB (Cohort 1C) or RPV (Cohort 1R), in addition to cART, which, passing safety and PK guidelines, are recommended as dosing for Cohort 2. Cohort 1C and Cohort 1R assignment is based on the adolescent’s pre-study cART regimen.

- **Cohort 1C:** Up to 30 adolescents to achieve approximately 20 evaluable for CAB. The evaluable population 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 1R:** Up to 25 adolescents to achieve approximately 15 evaluable for RPV. The evaluable population 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, to achieve approximately 70 evaluable, who had not previously participated in Cohort 1, receiving the final recommended oral 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.

Up to 60 parents or caregivers of adolescent participants, as selected by the protocol team, to complete a single qualitative phone interview.

**Note:** For definition of 'evaluable participant', please refer to Section 9.1 (General Design Issues) of the protocol.
Study Product:

**Cohort 1:**
- 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).

Dose adjustments are not anticipated but may occur as described in protocol Section 9 and 10.

**Cohort 2:**
- 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 once every four weeks for 92 weeks (for CAB LA 600 mg first injection and 400 mg subsequent injections; for RPV LA 900 mg first injection, 600 mg subsequent injections) during Step 4 injection phase.

Cohort 2 doses may change based on experience in Cohort 1, in which case, the new doses will be specified in a letter of amendment or full amendment.

Duration of Follow-Up:

Adolescents in Cohort 1 will be followed for up to 64 weeks. Adolescents will be followed for at least four weeks in Step 1 (oral phase) and at least 12 weeks in Step 2 (injection phase). All Step 2 adolescents will be followed (on cART, off study product) for up to an additional 48 weeks as part of long-term safety and washout PK follow-up after their last study product injection. Cohort 1 participants may continue study participation in Cohort 2, if eligible, prior to completing long-term safety and washout PK follow-up.

Adolescents in Cohort 2 will be followed for up to 144 weeks. Adolescents will be followed for at least four weeks in Step 3 (oral phase) and 92 weeks in Step 4 (injection phase). After completing 92 weeks of follow-up in Step 4 (injection phase), Cohort 2 adolescents may continue access to injectable study products through a mechanism external to the protocol, and will exit the study. Adolescents who permanently discontinue injectable study product use at any time during Cohort 2 Step 4, or not continuing to access the study products through the external mechanism, will be followed (on cART, off study product) for an additional 48 weeks as part of long-term safety follow-up after their last study product injection.

Enrolled parents/caregivers will complete a single qualitative phone interview.

Study Duration:

Approximately 5 years total. Accrual into Cohort 1 is expected to require approximately three months. Following review of data from Cohort 1 through Week 16, accrual into Cohort 2 is expected to require approximately nine months. Adolescents in Cohort 2 will be followed for up to three years.
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

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

Secondary Objectives: Cohort 1

- 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

Secondary Objectives: Cohort 2

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

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

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

Other Objectives

- To evaluate the tolerability and acceptability of CAB LA + RPV LA through Week 24, through Week 48, and through Week 96 in HIV-infected, virologically suppressed adolescents (Cohort 2)

- To evaluate the safety, antiviral and immunologic activity, and characterize PK of CAB LA + RPV LA through Week 96 in HIV-infected, virologically suppressed adolescents (Cohort 2)

- To evaluate adolescent participant’s experience of CAB LA and/or RPV LA, and parent/caregiver’s experience and perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA (Cohort 1 and Cohort 2)

- To evaluate the tolerability and acceptability, and characterize long-term safety and PK through 48 weeks following permanent discontinuation of CAB LA or RPV LA (Cohort 1)

- To evaluate the tolerability and acceptability, and characterize long-term safety and PK through 48 weeks following permanent discontinuation of CAB LA + RPV LA (Cohort 2)

- To describe HIV-1 resistance in participants experiencing virologic failure (Cohort 1 and Cohort 2)
Figure 1. Overview of Study Design for Cohort 1 Participants

**Cohort 1**
- CAB (Cohort 1C target n = 20 evaluable) or RPV (Cohort 1R target n = 15 evaluable)
- Accrual opens for both Cohort 1C and Cohort 1R concurrently and continues during interim analysis (no pause)
- Continue cART during Step 1, Step 2, and continue during LSFU

**Step 1**: 4-6 weeks of oral lead-in
- Visit Entry: Week 1, and Step 1a
  - Daily Oral CAB or RPV
  - PK Evaluations, Safety Evaluations, Adherence Assessments, Acceptability/Tolerability Assessments, CD4, HIV-1 RNA, Stored plasma for resistance
  - Safety through Week 4a visit will be reviewed for participant eligibility of injectable study product
  - Eligible or Not Eligible: Early Termination Visit

**Step 2**: 12 weeks
- Visits: Weeks 4b, 5, 6, 8, 9, 10, 12, 13, 14, and Week 16
  - Last oral dose: Week 4b only
  - IM injection of CAB LA or RPV LA: Week 4b (Step 2 Entry), Week 8, Week 12
  - PK Evaluations, Safety Evaluations, Adherence Assessments, Acceptability/Tolerability Assessments, CD4, HIV-1 RNA, Stored plasma for resistance
  - Qualitative Interview (selected participants only)

**LSFU**: Up to 48 weeks
- Visits: LSFU Week 4, 12, 24, 36, and LSFU Week 48
  - Permanent discontinuation of injectable study product during Step 2 or completion of Step 2 Week 16 visit
  - Long-term Safety and Washout PK Follow-up (LSFU)
  - Washout PK Evaluations, Safety Evaluations, Adherence Assessments, Acceptability/Tolerability Assessments, HIV-1 RNA, Stored plasma for resistance
  - Qualitative Interview (selected participants only)

**Interim Analysis**
- Cohort 1C n = 8 and Cohort 1R n = 8
- CMC will evaluate safety and PK through Week 16 to determine if criteria for opening Cohort 2 to accrual is met

**Criteria Met**
- SMC Review

**Criteria Not Met**
- CMC will:
  - Adjust the dose and newly enroll participants to evaluate safety and PK on the adjusted dose (Cohort 1C n = 8 and Cohort 1R n = 8)
  - OR
  - Continue current dose
  - OR
  - Stop study

**Cohort 2 Opens to Accrual only for Cohort 1 participants**
- Eligible Cohort 1 participants may rollover into Cohort 2
- Cohort 1 participants ineligible for Cohort 2 will complete all LSFU visits

**Cohort 1 Analysis**
- Cohort 1C n = 20 evaluable and Cohort 1R n = 15 evaluable
- CMC will evaluate safety and PK to determine if criteria for opening Cohort 2 to accrual for study-naive participants is met
Figure 2. Overview of Study Design for Cohort 2 Participants

**Cohort 2**

**CAB + RPV** (target n = at least 70 evaluable who have not previously participated in Cohort 1; former Cohort 1 participants may also enroll into Cohort 2)

Accrual first opens only for former Cohort 1 participants based on Cohort 1 interim analysis; then opens for new participants based on Cohort 1 full analysis

---

**Discontinue cART during Step 3 and Step 4 (resume cART during LSFU)**

### Step 1: 4.6 weeks of oral lead-in

Visits: Entry, Week 2, and Week 4a

Daily Oral CAB + RPV

- PK Evaluations, Safety Evaluations, Adherence Assessments,
- Acceptability/ Tolerability Assessments, CD4, HIV-1 RNA, Stored plasma for resistance

Safety through Week 4a visit will be reviewed for participant eligibility of injectable study products

- Eligible
- Not Eligible: Early Termination Visit

### Step 2: 9.2 weeks

Visits: Week 4b, every 4 weeks thereafter through Week 96

**Last oral dose:** Week 4b only

**IM injections of CAB LA + RPV LA:** Week 4b (Step 4 Entry), every 4 weeks thereafter through Week 96 (inclusive)

- PK Evaluations, Safety Evaluations, Adherence Assessments,
- Acceptability/ Tolerability Assessments, CD4, HIV-1 RNA, Stored plasma for resistance

- Qualitative Interview (selected participants only)

### Step 3: 48 weeks

Visits: LSFU Week 4, 12, 24, 36, and LSFU Week 48

Permanent discontinuation of injectable study product during Step 4 participation, or if not continuing injections (external to the study) after the Week 96 visit.

### Step 4: 48 weeks

Visits: LSFU Week 4, 12, 24, 36, and LSFU Week 48

---

**Long-term Safety and Washout PK Follow-up (LSFU)**

- Participants resume cART

- Washout Evaluations, Safety Evaluations, Adherence Assessments,
- Acceptability/ Tolerability Assessments, HIV-1 RNA, Stored plasma for resistance

- Qualitative Interview (selected participants only)
# Figure 3. Overview of Study Participation Flow for Cohort 1 Participants

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Step 1 (oral phase)</th>
<th>Step 2 (injection phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT 1 Screen</td>
<td>CT 1 Entry</td>
<td>CT 1 Wk 4b (Step 2 Entry)</td>
</tr>
<tr>
<td>CT 1 Entry</td>
<td>X</td>
<td>*</td>
</tr>
</tbody>
</table>

**Study Product**
- Dispense oral study product (for up to 6 wks):
  - X
  - *
  - *
- Administer injection study product:
  - X
  - X
  - X
  - X

**Pharmacology Evaluations**
- PK Sampling:
  - X
  - X
  - X
  - X
  - X
  - X
  - X
  - X
  - X

*If indicated

Cohort 1 participants will be followed per the LSFU visit schedule upon permanent product discontinuation, including completion of injectable study product regimen.

Cohort 1 participants who complete the Week 16 visit will skip the 4 weeks post-last IM visit during LSFU.

## Long-Term Safety and Washout PK Follow-Up (LSFU)

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>LSFU Week 4</th>
<th>LSFU Week 12</th>
<th>LSFU Week 24</th>
<th>LSFU Week 36</th>
<th>LSFU Week 48/ Early Termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK Sampling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Eligible Cohort 1 participants may rollover into Cohort 2 prior to completing all LSFU visits, or after exiting Cohort 1 (i.e. resume study participation).

See Figure 4 for continued participant flow into Cohort 2.
**Figure 4. Overview of Study Participation Flow for Cohort 2 Participants**

Eligible Cohort 1 participants may rollover into Cohort 2 prior to completing all LSFU visits, or after exiting Cohort 1 (i.e. resume study participation).

Study-naive participants will enroll into Cohort 2 after the Cohort 1 analysis.

### Cohort 2 (CT 2)

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>CT 2 Screen</th>
<th>Step 3 (oral phase)</th>
<th>Step 4 (injection phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT 2 Entry</td>
<td>CT 2 Wk 2</td>
<td>CT 2 Wk 4b (Step 4 Entry)</td>
</tr>
<tr>
<td>Study Product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense oral study product (for up to 6 wks)</td>
<td>X</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Administer injectable study products</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*if indicated

Participants continuing injections (external to the study) will exit at the Week 96 visit.

Participants will be followed per LSFU visit schedule upon permanent discontinuation of injectable study product during Step 4, or if not continuing injections (external to the study) at the Week 96 visit.

### Long-Term Safety and Washout PK Follow-Up (LSFU)

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>LSFU Week 4</th>
<th>LSFU Week 12</th>
<th>LSFU Week 24</th>
<th>LSFU Week 36</th>
<th>LSFU Week 48/ Early Termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Sampling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 Background

Contemporary antiretroviral therapy (ART) for management of HIV infection includes many potent, safe dosing options, some of which are available for adolescents and adults as one-pill, once-a-day, combination ART regimens. The long term success of HIV treatment remains dependent upon sustaining adherence to daily ART, which can be challenging (1, 2). In pediatrics, this is often further nuanced by factors specific to adolescents and their caregivers (3). Successful progression through the continuum of HIV care is poorer among adolescents than adults in the US, with as many as 43% failing to reach and sustain HIV viral suppression (VLS) (4). Unstructured treatment interruptions are a major issue for youth with perinatally acquired HIV-1 infection, with medication fatigue being the most common cited reason for such interruptions (5). While the current ART standard of care includes a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) plus another antiretroviral (ARV), alternative approaches are being examined that simplify treatment, reduce lifelong drug exposure and drug burden, preserve future treatment options, and minimize or avoid ART toxicities, particularly NRTIs. Regimens being explored are "NRTI-reducing" or "NRTI-sparing", including two-drug ART (from two independent classes) as initial treatment or a switch strategy (in virologically suppressed individuals). (6)

Long-acting (LA) injectable antiretrovirals are promising new therapies both for HIV treatment (7) and HIV prevention (8) that may change the treatment paradigm, although present unique implementation challenges. If proven safe and efficacious, these monthly/bi-monthly intramuscular (IM) injections, and other parenteral long-acting ART drug delivery platforms, could provide options to the current daily oral ART standard of care. These regimens would potentially optimize treatment adherence and ultimately maximize the benefits of ART. This approach is similar to modern contraceptive product development, which has greatly expanded client choices and includes a diversity of drug delivery options, such as oral tablets, intramuscular injections, long-acting implants and skin patches.

Cabotegravir (CAB) is a potent integrase strand transfer inhibitor (INSTI) with attributes that allow formulation and delivery as a LA parenteral product. Rilpivirine (RPV), also formulated as a LA product, is a diarylpyrimidine derivative and a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild type HIV-1 and select NNRTI-resistant mutants. Long-acting nanocrystal suspensions of CAB LA and RPV LA have been shown in clinical trials in HIV-infected adults to be safe, well tolerated and efficacious as a dual injectable ART in treatment-naïve settings (step down, maintenance therapy after an oral three drug ARV induction therapy (9) (Phase 3 Clinical trial ongoing; ClinicalTrials.gov Identifier: NCT02938520). A Phase 3 clinical trial of CAB LA plus RPV LA as a dual therapy approach in treatment experienced, virologically suppressed individuals is ongoing [ClinicalTrials.gov Identifier: NCT02951052]. A two-drug combination therapy with CAB LA plus RPV LA may offer comparable, if not a better tolerability and resistance profile, as well as improved adherence and treatment satisfaction in virologically suppressed patients (9).

Building on the experience to date with CAB LA and RPV LA in HIV-infected adults, IMPAACT 2017 Cohort 1 will assess the safety and PK of sequentially dispensed oral CAB followed by CAB LA (Cohort 1C), as well as oral RPV followed by RPV LA (Cohort 1R) in HIV-infected, virologically suppressed adolescents who continue their oral cART regimen. IMPAACT 2017 Cohort 2 will then establish if HIV-1 infected, virologically suppressed adolescents remain suppressed upon switching to a two-drug intramuscular (IM) regimen of CAB.
LA plus RPV LA. The initial age studied will be adolescents aged 12 to <18 years, and results from this group may inform a protocol amendment to this study for a younger population, aged 6 to < 12 years.

1.2 Prior Research

1.2.1 Cabotegravir

Cabotegravir (GSK1265744) is an investigational HIV INSTI that has attributes favorable for both HIV treatment and prevention indications. CAB is being developed as both oral and long acting injectable formulations.

CAB is rapidly absorbed following oral administration of the micronized tablet formulation, with median tmax observed 2 to 3 hours post dose in the fasted state. Co-administration of single dose CAB 5 mg and 30 mg tablets with a moderate fat meal demonstrated minimal impact (<15% increase in CAB AUC(0-∞) and no impact on Cmax. In clinical studies to date, CAB tablets were taken without regard to the timing of or type of food consumed. CAB half-life of 35 to 42 h has been noted following oral administration. (10)

As of August 2017, there is no previous clinical trial experience with oral CAB or CAB LA in humans under 18 years of age. To date, CAB LA is a 200 mg/mL nanosuspension that has been administered as an IM injection and a SC injection of single doses of 100 to 800 mg and repeat doses from 200 to 800 mg. CAB LA exhibits absorption-limited (flip-flop) kinetics, and CAB has been detected in plasma up to 52 weeks or longer after administration of repeat IM injections of CAB LA. Due to limited sampling, the observed apparent tmax is generally observed at approximately one week post IM injection in Phase 2 studies. Apparent terminal phase t½ following CAB LA reflects absorption and ranges from approximately 18 to 50 days. Steady state appears to be achieved by 20 to 40 weeks of the first IM injection of CAB LA Q4W or Q8W regimens. Variability in CAB Cmax following CAB LA is moderate to high with CV% ranging from 30 to >100%, due to variability in absorption rate. However, AUC(0-∞), which reflects the extent of absorption rather than the rate of absorption, exhibits lower variability with CV% ranging from 12 to 53%. In addition, variability decreases upon repeat administration.(10)

Following oral administration in humans, CAB is primarily eliminated through metabolism, and renal elimination of unchanged CAB represents less than 1% of the total dose administered. In vitro and in vivo data indicate that CAB is primarily metabolized by UGT1A1 with some involvement from UGT1A9. CYP-mediated CAB metabolism is expected to be minimal as evidenced by the lack of effect observed when co-administered with etravirine (ETV), a known CYP3A4 inducer, in human subjects. Cabotegravir is the predominant circulating compound in plasma, representing > 90% of plasma total radiocarbon. Fifty-eight percent of the total oral dose is excreted as unchanged CAB in the feces and 26.8% of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (75% of urine radioactivity, 14% of total dose).(10)

In a population PK analysis combining data from eight studies, gender was found to be a significant covariate affecting the absorption rate following administration of CAB LA. Females were observed to have a slower absorption rate than males with the injectable formulation only.(10)

In a population PK analysis combining data from eight studies, BMI was found to be a significant covariate affecting the absorption rate following administration of CAB LA. A low BMI was
associated with a faster absorption rate and a high BMI was associated with a slower absorption rate. This effect was not observed following oral administration. (10)

CAB LA has been administered intramuscularly to healthy and HIV infected adults at doses of 100mg to 800mg. In HIV-infected subjects, CAB LA has maintained virologic suppression on a maintenance dose of 400mg IM Q4W injections in conjunction with RPV LA (200056). The population PK model described above included IM data in 416 adults (12% female). Gender and BMI were significant covariates affecting the absorption rate constant following IM administration, such that absorption was slower in females than males and in subjects of larger BMI (up to 60kg/m²). The slower absorption in females and high BMI participants resulted in lower peaks and higher troughs and was not associated with clinical outcome differences. Potential participants with high BMI will be excluded from Cohort 1 to ensure precise in PK parameters but high BMI will not be an exclusion for Cohort 2.

CAB has no reported significant effect on cardiac repolarization. (10)

Summary of cabotegravir safety data:

CAB has been generally well tolerated as single or repeated doses in clinical studies of healthy adult subjects. In total, 1644 participants have received at least 1 dose of CAB in completed or ongoing studies (oral and/or long-acting injection) through April 01, 2017. This includes 838 participants who have received CAB as a long-acting injection (CAB LA).

A meta-analysis of safety data from 14 completed phase I/IIa studies has been performed for the CAB development program (11). In this meta-analysis, a total of 423 subjects including 408 healthy subjects and 15 HIV-infected subjects were exposed to CAB oral and/or LA, of whom, 136 subjects received CAB LA. Of the total of 423 subjects, 127 were females and 296 males, with a median age of 32 years (range 18-64). Thirty-three subjects, with a median age of 31 years (range 18-54), received placebo and were included in the meta-analysis. No deaths, non-fatal drug-related SAEs, or pregnancies were reported. No subjects developed a severe or Grade 3 AE related to CAB. One seizure occurred in the LAI116815 study in a subject with pre-existing history of seizure. The seizure occurred approximately 9 months after a single dose of CAB 400mg IM, and approximately six months after CAB was no longer detectable in the serum. The seizure in this subject was not considered by the Investigator or the Sponsor to be related to CAB. Adverse events were reported at all studied doses. The most frequent (≥5%) non-injection site reaction (ISR) AEs were headache (overall rate of 16%: 10% in oral and 27% in LA) which occurred more frequently than in placebo subjects (11%) and upper respiratory tract infection (overall rate of 6%: 2% in oral and 12% in LA) versus none in placebo subjects. CAB was well tolerated across all studies with overall 13% of any drug-related AEs and few drug related withdrawals. (11)

Injection site reactions (ISRs) associated with CAB LA injection were very common (IM: 77% of exposed subjects, SC: 96% of exposed subjects) but generally mild with no Grade 3 or Grade 4 ISR-AEs. The most frequent ISRs for IM and SC dosing, respectively, were pain, erythema and nodules; the incidence of nodules was higher with SC dosing (79% of subjects) in comparison with IM dosing (19% of subjects). ISRs did not interfere with daily activities. Median IM ISR duration was ≤ 7 days for pain and erythema and approximately 19 days for nodules. The following treatment emergent ≥Grade 2 elevations in lab values were reported: total cholesterol (7%), lipase (4%), creatine phosphokinase (CPK) (2%) and bilirubin (2%). A subject in the LAI115428 study, developed a Grade 1 ALT elevation of 4.3x ULN 118 days after initiation of
CAB and 41 days after administration of RPV LA, that was considered not related to study drug and resolved while on both drugs. (10)

No pre-clinical signal for renal toxicity has been demonstrated and findings in humans have not been associated with clinically evident renal dysfunction or proteinuria (10).

Occurrences of asymptomatic, transient instances of elevations of CPK levels have been observed in Phase 1 studies and Phase 2b studies with CAB. These generally appeared to be related to physical activity, were not associated with clinical symptoms, and returned to pre-treatment levels in all cases. No subject has required discontinuation of treatment with CAB as a result of a CPK elevation. A small number of subjects with CPK elevations in a completed PrEP study did not transition from oral treatment in the lead in phase to injection, as a precautionary measure, since a causal relationship to CAB could not be ruled out. Rhabdomyolysis of uncertain cause has been included in labelling for a currently available integrase inhibitor (raltegravir). A single report of rhabdomyolysis involving a subject receiving CAB was strongly confounded by use of an illicit drug (3,4-Methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, with concurrent physical exertion and dehydration. (10)

Residual concentrations of CAB remain in the systemic circulation of subjects who stop HIV treatment (e.g. for tolerability issues or treatment failure) for prolonged periods (up to 12 months or more) (10). Subjects discontinuing an LA regimen may be at risk for developing viral resistance to CAB many weeks after discontinuing injectable therapy; therefore, adoption of an alternative, fully suppressive antiretroviral regimen is essential.

**Summary of side effects observed and/or monitored for in patients on cabotegravir include:**

**Hepatobiliary disorders**
Four subjects with possible or probable drug induced liver injury (DILI) related to CAB have been identified in the Phase 2b HIV treatment studies. Three of these subjects met liver stopping criteria 4-8 weeks after initiation of oral treatment with CAB (60 mg n=2, 30 mg n=1). The fourth subject met liver stopping criteria after having received approximately 44 weeks of treatment with oral CAB 30 mg. In all cases subjects remained asymptomatic, did not develop hepatic dysfunction and liver aminotransferase elevations returned to normal or approached pre-treatment levels following withdrawal of all antiretroviral treatment. A role of CAB in these cases could not be ruled out. One of the four subjects, with ongoing active chronic hepatitis C infection, developed a concomitant increase in total and direct bilirubin. This subject had underlying liver fibrosis. The three remaining subjects had evidence of hepatosteatosis on liver imaging - which may have been pre-existing (10).

Studies to date have incorporated close monitoring of liver chemistries and have adopted liver stopping criteria. Subjects with known and documented Hepatitis B or Hepatitis C infection, with clinically relevant hepatic disease, or ALT Grade 3 or higher are excluded from IMPAACT 2017, per Section 4. Additionally, studies to date involving exposure to the long acting injection have incorporated an oral lead-in period as a precautionary measure to reduce the risk of severe hypersensitivity (see below) or liver injury developing during exposure to the LA formulation.

**CAB Injection only:** ISRs are very common, but generally mild or moderate, most frequently comprising pain at the injection site, with localized erythema, pruritis, warmth, swelling, nodule formation, induration or bruising occurring less commonly. To date, most reactions have been self-limited. (10)
Hypersensitivity reactions
Hypersensitivity reactions have not been reported with cabotegravir but have been reported in association with other integrase inhibitors including the closely related compound, dolutegravir. These reactions were characterized by rash, constitutional findings and sometimes organ, including liver, dysfunction. However, no such reactions have been observed to date in association with CAB. An oral lead-in is being implemented within clinical studies to reduce the risk of a hypersensitivity reaction occurring following the initiation of LA therapy. (10)

Use in pregnancy: Data in pregnancy are limited. Non-clinical data from rat pre- and postnatal (PPN) studies have indicated reduced survival and viability rates amongst rat pups during the first 4 days of life at the maximum tested dose of 1000 mg/kg/day (maternal exposure). No-observed-adverse-effect-level (NOAEL) was established at the mid dose 5 mg/kg/day, which remains >20 fold predicted Cmax and AUC exposures for anticipated clinical CAB LA exposures. The clinical significance of these findings is unknown. (10)

Suicidal Ideation and Behavior Monitoring:
CAB exposure has not been associated with an increased risk of suicidal ideation or psychiatric disorders however, patients with HIV infection or those in some high-risk categories for HIV acquisition may occasionally experience symptoms of depression and/or suicidal ideation or behavior. In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some patients being treated with INSTIs. Dolutegravir (DTG) (a closely related integrase inhibitor) has been associated with reports of suicidal ideation or behavior (particularly in patients with a pre-existing history of depression or psychiatric illness). (10)

Seizures:
Overall, there is not convincing evidence that CAB exposure may be causally associated with seizure or with reduction of seizure threshold, due to the low frequency of reports, the confounders present in the cases received to date and lack of any pre-clinical signal or identified plausible mechanism. Three cases of seizures have been documented in the CAB programme cumulatively through 01 October 2016. Two of the cases occurred in HIV uninfected subjects with a prior history of seizure and one case involved a subject in study 200056 with circumstantial and anecdotal evidence of illicit drug use. (10)

Dolutegravir and Pregnancy
Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) in the same class of pharmaceuticals as CAB. Thus far, limited safety or efficacy data for DTG in pregnancy in humans have been published or presented. In May 2018, WHO and several other regulatory agencies released advisories regarding the safety of DTG in early pregnancy (12).

This was based on information received from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study, the largest body of data related to birth outcomes following the use of DTG in pregnancy. This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Botswana’s HIV program moved to universal ART with DTG/TDF/FTC in first line for patients starting ART (including pregnant women) in May of 2016 (women already on other regimens were not switched to DTG). The previous first-line regimen was EFV/TDF/FTC. Almost all women on DTG-based and EFV-based ART took these drugs in combination with TDF/FTC. More than 95% of women in Botswana deliver in a hospital, and obstetric records were available for >99% of women. The Tsepamo surveillance study is conducted at 8 of the largest public maternity
wards across Botswana (representing ~45% of the total births in the country). Research assistants abstracted exposure data from the maternity card for all consecutive in-hospital deliveries (both HIV-infected and HIV-uninfected women). Each newborn, whether stillborn or live-born, undergoes a systematic infant surface examination that is completed by trained nurse midwives. Reports and photographs (where available) of major abnormalities are reviewed by an experienced medical geneticist who is blinded to exposure information. During a preliminary unscheduled analysis of the Tsepamo data collected between August 15, 2014 and May 1, 2018, which was undertaken at the request of colleagues who were preparing for a WHO meeting, the investigators found 4 cases of neural tube defects in babies of 426 women who became pregnant while taking DTG (prevalence 0.9%). This rate compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception. Data is expected on the pregnancy outcomes of an additional 600 women in the Tsepamo study who were taking DTG around the time of conception. More data are also expected to be forth coming from other studies of DTG in pregnancy. These data will provide more information on the safety of DTG for women of childbearing age.

Cabotegravir is not dolutegravir. While these medications share a common molecular backbone, and have a similar mechanism of activity, they are separate chemical compounds and have differences in antiviral activity, pharmacokinetics, metabolism and drug-drug interactions. It is not known if the safety signal identified with DTG will be confirmed in other studies and/or settings where DTG is being used or observed with CAB. CAB was evaluated in a complete package of reproductive toxicology studies, including embryofetal development studies, and no safety findings suggestive of teratogenesis or neural tube defects were identified as of the information included in the December 2017 version of the Investigator’s Brochure. Nevertheless, given limited experience with use of CAB in pregnancy, as a precautionary measure, women of reproductive potential are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies following exposure to CAB LA.

1.2.2 Rilpivirine

Rilpivirine (TMC278, RPV) is a NNRTI with in vitro activity against wild type and NNRTI resistant HIV 1. Rilpivirine 25-mg once daily (oral tablet) is approved for the treatment of HIV-1 infection in ART-naïve patients 12 years of age and older in multiple countries including the United States of America (USA), the European Union (EU), Canada, and Japan as EDURANT®(13). In most countries, including the USA and EU, this indication is further restricted to patients with a plasma viral load (VL) ≤100,000 HIV-1 ribonucleic acid (RNA) copies/mL. RPV (dose 25 mg) as part of a once-daily single-tablet oral regimen is also approved for adults and adolescents in several countries as Complera®/Eviplera® (emtricitabine [FTC]/RPV/tenofovir disoproxil fumarate[TDF]) or Odefsey® (FTC/RPV/tenofovir alafenamide[TAF]).

A parenteral long acting formulation of RPV (RPV LA) is in Phase III of development, in combination with a parenteral long acting formulation of CAB (CAB LA). Of note both the oral and injectable formulation of RPV needs to be protected from direct exposure to light and is dispensed accordingly. Up to January 2017, in total, 160 healthy volunteers participated in studies with the long acting (LA) injectable form of RPV of whom 128 received RPV LA. Additionally, in 1 Phase IIb study, 230 HIV-1 infected adult subjects received RPV LA in combination with CAB LA.
The exposure to RPV as the tablet formulation was approximately 40- to-50% lower when taken under fasting conditions or with only a nutritional drink as compared to intake with a standard or high fat breakfast. Therefore, oral RPV must always be taken with a meal.\(^{(14)}\)

The exposure to RPV can be affected by modulators of CYP3A4-enzyme activity and by drugs that increase the gastric anti-logarithmic proton concentration (pH), the latter being only applicable to oral RPV. Proton pump inhibitors (e.g. omeprazole) should not be co-administered with oral RPV as this will decrease the exposure to RPV due to the increase in gastric pH. H2-receptor antagonists, however, can be used if administered either at least 12 hours before or at least 4 hours after intake of RPV, and antacids can be used if administered either at least 2 hours before or at least 4 hours after intake of RPV. Drugs that induce CYP3A4 activity (e.g. rifampin, carbamazepine) can reduce the RPV exposure (either as oral or LA formulation) and should not be co-administered. Rifabutin can be co-administered with oral RPV, provided that the oral RPV dose is increased to 50 mg q.d. throughout co-administration. Drugs that inhibit CYP3A4 activity (e.g. ketoconazole, boosted protease inhibitors [PIs]) can increase the exposure to RPV (either as oral or LA formulation) but do not require dose adjustments.\(^{(14)}\)

The approval of oral RPV 25 mg once daily for adolescents was based on the results of study TMC278-TiDP6-C213. The 48-week results of the adolescent cohort (N=36) in this study demonstrated that treatment with RPV 25 mg once daily, in combination with an investigator-selected background regimen, is efficacious, generally safe and well tolerated in adolescents of ≥12 to <18 years of age\(^{(15)}\).

The 25 mg once daily dose in adolescents resulted in similar RPV exposure as observed in adults. Also, no apparent relationships were observed between the RPV pharmacokinetics and efficacy or safety parameters in adolescents at Week 48. In the adult trials with the RPV doses of 25 mg once daily, no clear effect of body weight on the RPV exposure was seen. Similarly, data in adolescents between 12 and 18 years of age weighing approximately 33 to 93 kg also showed no effect of body weight on the RPV exposure.\(^{(15)}\)

Oral RPV 25mg has been co-administered with oral CAB in one Phase 1 study in healthy subjects and two Phase 2 studies of HIV infected subjects. Study LAI116181 (ClinicalTrials.gov Identifier: NCT01467531) showed that there was no relevant drug interaction between CAB and RPV.\(^{(14)}\)

Population pharmacokinetic analysis of RPV in HIV infected patients indicate that race has no clinically relevant effect on the exposure to RPV. No clinically relevant differences in the pharmacokinetics of RPV have been observed between men and women.\(^{(14)}\)

The pharmacokinetics of RPV have not been studied in patients with renal insufficiency. Renal elimination of RPV is negligible. Therefore, the impact of renal impairment on RPV elimination is expected to be minimal. As RPV is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. No dose adjustment of RPV is required in patients with renal impairment.\(^{(14)}\)

RPV is primarily metabolized and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child Pugh score B) to 8 matched controls, the multiple dose exposure of RPV was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. No dose adjustment is required in patients with mild hepatic impairment.
or moderate hepatic impairment. RPV has not been studied in patients with severe hepatic
impairment (Child Pugh score C). (14)

The effect of RPV at the recommended dose of 25 mg q.d. (marketed dose) on the QT interval
corrected for heart rate according to Fridericia (QTcF) interval was evaluated in a randomized,
placebo and active (moxifloxacin 400 mg q.d.) controlled crossover study thorough QT (TQT) in
60 healthy adults, with 13 measurements over 24 hours at steady state. RPV at the recommended
dose of 25 mg q.d. is not associated with a clinically relevant effect on QTc. Higher doses of
RPV (75 and 300 mg q.d., 3 and 12 times higher than the recommended dose, respectively)
examined in a previous TQT study, were associated with mean maximum QTcF prolongations >
10 ms, which were dose and plasma concentration dependent. Plasma concentrations after
administration of RPV LA are substantially lower than those obtained with 75 mg q.d. and 300
mg q.d. and comparable to or lower than the plasma concentrations achieved with RPV 25 mg
q.d. given orally. Therefore, no clinically relevant increase in QTcF is expected with the plasma
concentrations achieved with RPV LA. In the RPV LA studies performed in healthy subjects, no
increases in QTc have been seen. (14)

Data on pregnancy and lactation remain limited; the prescribing information recommends that
RPV should be used during pregnancy only if the potential benefit justifies the potential risk and
that the mothers should be instructed not to breastfeed if they are receiving RPV (13). RPV in
combination with a background regimen was evaluated in the RPV treatment arm of study
TMC114HIV3015, in 19 pregnant women during the second and third trimesters, and postpartum.
RPV was well tolerated during pregnancy and postpartum. There were no new safety findings
compared with the known safety profile of RPV in HIV-1 infected adults. (14)

RPV LA (formulation G001) has been administered intramuscularly (IM) to healthy and HIV
infected adults at doses of 300 mg to 1200 mg. RPV pharmacokinetic parameters following
successive monthly intramuscular administration of 1200/600/600 mg RPV LA in the gluteal
muscle in healthy adult subjects showed a half-life of 91 days +/- 41 days (t1/2; mean +/- SD)
(14). In HIV-infected subjects, RPV LA maintained suppression of viral load following monthly
(Q4W) IM injections of 600 mg or bi-monthly (Q8W) injections of 900 mg, in conjunction with
CAB LA monthly or bi-monthly (LATTE-2 [ClinicalTrials.gov Identifier: NCT02120352]) (9).
Currently, a dosing regimen of a RPV LA 900 mg IM loading dose followed by Q4W IM
injections of 600 mg, in conjunction with CAB LA Q4W, is being evaluated in two Phase 3
studies in adults (ATLAS [ClinicalTrials.gov Identifier: NCT02951052] and FLAIRE
[ClinicalTrials.gov Identifier: NCT02938520]). Adverse events with 'injection site pain' and
'injection site reaction' have occurred with RPV LA injection (with the G001 formulation which
was selected for further development). All these events were grade 1 or grade 2 in severity and
were considered by the investigator to be at least possibly related to study medication. (14)

**Summary of side effects observed and/or monitored for in patients on rilpivirine include:**

*Skin events*
Some observations of grade 1 and 2 rashes with oral RPV have been reported in clinical studies
executed to date, but no grade 3 or 4 skin events. (14)

*Nervous System Events*
Nervous system-related events, predominantly headache and to a lesser extent dizziness, have
been reported with RPV in clinical studies executed to date. Additionally, there have been reports
of delusions and inappropriate behavior in patients receiving first generation NNRTIs, especially
in patients with a history of mental illness or substance use. Severe acute depression (including suicidal ideation/attempts) has also been reported in patients receiving NNRTIs. (14)

Further details about oral rilpivirine can be obtained from the FDA approved full prescribing information sheet. (13)

1.2.3 Clinical trial experience using cabotegravir plus rilpivirine as a dual antiretroviral therapy regimen

Two Phase IIb studies [Study LAI116482 [LATTE] (16) and Study [LATTE-2] (9)] have been conducted with oral CAB and/or IM CAB LA and oral RPV and/or IM RPV LA, evaluating an induction/maintenance simplification approach.

In the LATTE study, both male and female participants were randomized to oral CAB 10, 30, or 60 mg + two NRTIs compared to efavirenz (EFV) + 2 NRTIs. The study enrolled and treated 243 participants, 181 of whom received one of the three regimens of CAB plus 2 NRTIs and 62 of whom received EFV 600 mg once daily plus 2 NRTIs. Following 24 weeks of Induction therapy, participants receiving CAB who had achieved a HIV-1 RNA < 50 copies/mL (c/mL) simplified their ART regimen by discontinuing the NRTIs, initiating RPV, and continuing on two drug ART (CAB + RPV). A robust virologic response (HIV-1 RNA <50 copies/mL) was observed across all CAB plus NRTI treatment groups by the end of the 24-week induction phase (CAB subtotal: 156/181 [86%] vs EFV: 46/62 [74%] (ITT-E), with a shorter time to viral suppression for the CAB groups compared with the EFV group (each p<0.001; log-rank test). A planned Week 48 analysis (24 weeks of CAB + 2 NRTIs Induction, followed by 24 weeks of CAB + RPV Maintenance) demonstrated the proportion of participants with plasma HIV-1 RNA <50 c/mL (Snapshot algorithm), in each of the CAB plus RPV groups remained numerically higher than the EFV plus dual NRTI group at Week 48 (CAB: 149 [82%] vs EFV: 44 [71%]). Similar antiviral activity was observed across the three dosing arms of CAB in combination with RPV (10 mg: 80%; 30 mg: 80%; 60 mg: 87%, ITT-E, MSD=F), which compared favorably to EFV 600 mg plus 2 NRTIs (71%; ITT-E, MSD=F). (16)

Following 72 weeks of two-drug maintenance therapy (Week 96), 137 (76%) of CAB plus RPV patients and 39 (63%) of EFV plus dual NRTI patients remained virologically suppressed (ITT-E, MSD=F). (16)

An efficacy analysis of the ITT-Maintenance Exposed (ITT-ME) population which excludes participants who did not enter the Maintenance Phase, and assessed the ability of the two-drug oral regimen to maintain viral suppression was also performed at Week 96. In this population, virologic response (HIV-1 RNA <50 c/mL) was high across all treatment arms at Week 96, demonstrating a comparable durability of virologic response between treatments (CAB: 137/160 [86%]; EFV: 39/47 [83%]) with numerically higher values observed for the CAB 30 mg (45/53 [85%]) and 60 mg (51/55 [93%]) groups compared with the 10 mg group (41/52 [79%]). (16)

In summary the LATTE study results showed that cabotegravir plus dual NRTI therapy had potent antiviral activity during the induction phase in treatment naïve HIV infected adults and a two-drug maintenance therapy of cabotegravir plus rilpivirine provided antiviral activity similar to efavirenz plus dual NRTIs until the end of 96 weeks (16). These results provided the background to next look at the long acting injectable formulations of both CAB and RPV as a two-drug regimen for the treatment of HIV-1 infection in LATTE-2.
The LATTE-2 study (9) evaluated a 20 week induction of HIV-1 RNA suppression with a three drug oral antiretroviral regimen consisting of CAB + abacavir/lamivudine (ABC/3TC) Fixed Dose Combination (FDC) followed by randomization to a two-drug two-class regimen consisting of IM CAB LA + RPV LA compared to continuation of therapy with oral CAB + ABC/3TC for the maintenance of HIV-1 RNA suppression. A total of 309 participants were enrolled and treated. (9)

During the Induction Phase there was a rapid and sustained decline in HIV-1 RNA, with 91% of participants (282/309) achieving HIV-1 RNA <50 c/mL through 20 weeks of therapy. There was a single participant (with known compliance issues) with confirmed virologic failure during the Induction period. Virologic testing revealed no treatment emergent phenotypic or genotypic resistance in this participant. (9)

The primary endpoint for LATTE-2 was the Week 32 proportion of participants with HIV-1 RNA < 50 c/mL (Snapshot, Intent-to-Treat Maintenance Exposed population [ITT-ME]). Following virologic suppression on three drug oral therapy in the Induction Phase, 286 participants qualified to enter randomization at the Day 1 visit, and were subsequently randomized 2:2:1 onto once every 4 weeks IM injections with CAB LA + RPV LA (Q4W), once every 8 weeks (Q8W) IM injections with CAB LA + RPV LA or continuation of oral CAB + NRTIs, respectively. At the time of randomization at Day 1, participants entering one of the IM arms discontinued all oral ART. Through 32 weeks of two-drug maintenance therapy, 95% (Q8W) and 94% (Q4W) of participants on injectable dosing were virologic successes, compared to 91% of participants continuing three drug oral CAB + NRTIs, meeting pre-specified criteria for comparability between the dosing arms. (9)

Through 32 weeks of Maintenance therapy, there was one participant each on Q8W and oral dosing with Confirmed Virologic Failure (CVF), without any evolution of viral resistance. The CVF on Q8W dosing occurred following an aberrant RPV injection, without measurable plasma RPV concentrations 4 weeks post dosing. Between Week 32 and Week 48, one additional participant (Q8W) had confirmed virologic failure. This participant had a Baseline HIV-1 RNA of 444,489 c/mL. At Week 48, the participant was a suspected virologic failure with HIV-1 RNA = 463 c/mL. Upon retest, ten days later, the virologic failure was confirmed with HIV-1 RNA of 205 c/mL. At the time of CVF, this participant had treatment emergent NNRTI resistance K103N, E138G, and E238T, with high level phenotypic resistance to delavirdine (>MAX), efavirenz (48 fold change [FC]), nevirapine (>Max), and rilpivirine (3.34 FC). The fold change to etravirine (1.91) was below the lower cutoff. Week 48 integrase genotype had the treatment emergent integrase resistance mutation Q148R, with accompanying resistance to raltegravir (29 FC), elvitegravir (138 FC), and cabotegravir (6.06 FC). The Week 48 sample was not resistant to dolutegravir (1.38 FC). In total through week 96, three patients (1%) experienced protocol-defined virological failure (two in the 8-week group; one in the oral treatment group) of whom, one showed phenotypic resistance to rilpivirine and cabotegravir. (9)

Week 48 and week 96 were secondary endpoints for LATTE-2, and permitted the evaluation of the two-drug long-acting combinations’ ability to maintain the virologic suppression demonstrated at Week 32. At Week 48, 92% (Q8W) and 91% (Q4W) of participants receiving injectable dosing had a sustained virologic response (HIV-1 RNA <50 c/mL) compared to 89% of participants continuing oral CAB + 2 NRTIs (Figure 5) (9). At week 96, viral suppression was maintained in 47 (84%) of 56 patients receiving oral treatment, 100 (87%) of 115 patients in the 4-week group, and 108 (94%) of 115 patients in the 8-week group. (9)
Figure 5. Proportion of patients with HIV-1 RNA concentration less than 50 copies per mL (FDA snapshot algorithm) by visit at week 96 in the LATTE-2 study

<table>
<thead>
<tr>
<th>Study visit</th>
<th>Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)</th>
<th>Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)</th>
<th>Oral cabotegravir plus abacavir-lamivudine (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction period</td>
<td>Maintenance period</td>
<td>Maintenance period</td>
<td>Maintenance period</td>
</tr>
<tr>
<td>Outcomes (n, %) at 96 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virological response</td>
<td>100 (87%)</td>
<td>108 (94%)</td>
<td>47 (84%)</td>
</tr>
<tr>
<td>Virological non-response</td>
<td>0</td>
<td>5 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Data in window not below threshold</td>
<td>0</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Discontinued for other reason while below threshold</td>
<td>0</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>No virological data</td>
<td>15 (13%)</td>
<td>2 (2%)</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Discontinued due to adverse event or death</td>
<td>9 (8%)</td>
<td>1 (&lt;1%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
<td>5 (4%)</td>
<td>1 (&lt;1%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Of note, through 96 weeks, no patients in the 4-week group failed for virological reasons although one patient met virological non-response criteria at week 48 but subsequently re-suppressed. In comparison, in the 8-week group, nine patients met virological non-response at week 48 (HIV-1 RNA >50 copies per mL), four were re-suppressed with HIV-1 RNA less than 50 copies per mL at week 96 without a change in therapy. Of the five patients in the 8-week group with virological nonresponse at week 96, two had HIV-1 RNA of at least 50 copies per mL at week 96 (one of whom had HIV-1 RNA ≥50 copies per mL at week 48), one discontinued due to protocol-defined virological failure at week 4, one withdrew consent due to intolerability of injections at week 8, and one withdrew due to investigator discretion at week 48 while not suppressed (and subsequently confirmed as a protocol-defined virological failure). (9)

Overall CAB LA and RPV LA were well tolerated with injection site reactions being the most commonly reported AE. Serious adverse events occurred in 13 (11%) patients in each of the intramuscular treatment groups and nine (16%) patients in the oral treatment group, only one of which was considered drug related by the investigator (migraine, which occurred in the initial oral induction period of the study). 11 patients (4%) developed an adverse event during the maintenance period, which led to withdrawal: eight patients (7%) in the 4-week group, two (2%) in the 8-week group, and one (2%) in the oral treatment group. Two patients (both in the 8-week group) had injection site reactions leading to withdrawal within 8 weeks of initiating dosing. (9)
Through week 96, the vast majority of injection site reactions were due to pain/discomfort with nearly all injection site reactions classified as mild (3648 [84%] of 4360 injections) or moderate (673 [15%] of 4360 injections), rarely resulted in discontinuation (two [<1%][Q8 week arm] of 230 patients) and with median symptom duration of 3 days.

Serious adverse events during maintenance were reported in 22 (10%) of 230 patients in the intramuscular groups (4-week and 8-week groups) and seven (13%) of 56 patients in the oral treatment group; none was considered drug related. There was no discernible tolerability difference between Q4W (2 mL) dosing and Q8W (3 mL dosing).(9) The reported ISR AE incidence dropped significantly after the first injection (Figure 6) (17).

Figure 6. Injection Site Reactions (ISRs) for CAB LA or RPV LA over time through week 96 in the LATTE 2 study

**ISR for CAB LA or RPV LA Over Time**

- 99% of ISR events were mild (84%) or moderate (15%), and 89% resolved within 7 days
- Most common ISR events: pain (66%), nodules (8%), swelling (5%), and pruritus (6%)
- 2 of 230 subjects (<1%) had an ISR that led to discontinuation (QBW) through Week 96

Despite ISR, the overall participant satisfaction with treatment remained very high when assessed both at 48 and 96 weeks (Figure 7; Panels A and B respectively) (9). At week 96, patients reported very high levels of satisfaction across all three groups (4-week, 8-week, and oral treatment, via the HIVTSQ[s]), with 246 (97%) of 254 patients selecting a score of 5 or 6 on a 6-point satisfaction scale. While a similar percentage of patients in each of the intramuscular groups (≥99%; 99 of 100 in the 4-week group and 107 of 108 in the 8-week group) reported they would be highly satisfied to continue their current long-acting regimen, a lower percentage would elect to continue on oral dosing (78%; 36 of 46 patients in the oral treatment group). (9)
The most common non-ISR AEs were nasopharyngitis (39 patients [34%] in the 4-week group, 35 [30%] in the 8-week group, and 22 [39%] in the oral treatment group), diarrhea (32 [28%] in the 4-week group, 27 [23%] in the 8-week group, and 11 [20%] in the oral treatment group), and headache (27 [23%] in the 4-week group, 29 [25%] in the 8-week group, 14 [25%] in the oral treatment group). (9)

Two currently ongoing phase III studies, FLAIR (ClinicalTrials.gov Identifier: NCT02938520) and ATLAS (ClinicalTrials.gov Identifier: NCT02951052) are designed to evaluate CAB LA plus RPV LA for the treatment of HIV-1 infection in adults. In FLAIR, treatment-naive patients are given a 20-week daily oral dolutegravir/abacavir/lamivudine (Triumeq®) regimen, and then randomized to switch to a regimen of injectable CAB LA + RPV LA every 4 weeks, or remain on oral therapy. In ATLAS, treatment-experienced patients with suppressed viral load are randomized to switch from their existing cART to injectable formulations of CAB LA + RPV LA or remain on oral cART. Participants are from investigative sites across Africa, the Americas, Asia and Europe.
1.3 Rationale

The IMPAACT 2017 is a Phase I/II study being conducted to establish if adolescents (and later younger children), infected with HIV-1 who are currently virologically suppressed on ART, remain suppressed upon switching to a two-drug intramuscular (IM) long-acting (LA) regimen of CAB LA plus RPV LA. The initial age group studied will be adolescents aged 12 to <18 years, and results from this initial age cohort may inform the study details in a protocol amendment at a later date for a younger population.

1.3.1 Rationale for use of oral lead-in prior to injectable dosing

The CAB LA and RPV LA formulations have a pharmacokinetic decay rate that exposes the injected individual to detectable levels of cabotegravir and rilpivirine for up to 52 weeks after an injection. A 4-6-week lead-in period of daily oral (short acting) CAB and RPV prior to injectable administration, with serial safety assessments, will allow identification of any acute toxicity prior to administration of a non-dialyzable, non-removable depot injection. A similar oral lead-in period has been employed in previous trials using these LA formulations.

The oral lead-in period is also designed to provide uninterrupted study product coverage while awaiting the Week 4 safety laboratory test results, which will determine eligibility for receiving the LA formulations. The safety assessment is done towards the end of the 4-week oral lead-in and, for clarity, has been named the visit 4a study visit. Safety lab results from the 4a study visit will be reviewed and, if appropriate, the next visit will be scheduled as soon as possible to administer the first study injection; this next visit has been named visit 4b. This nomenclature has been adopted to promote consistency across the CAB/RPV studies and allow for clearer interpretation and comparisons. Given a participant population with a history of durable viral load suppression at and prior to study entry, a viral load assessment at the 2-week visit, and questionable clinical meaningfulness of a single HIV viral load blip, a repeat HIV viral load assessment is not part of the laboratory assessments done at visit 4a to approve giving the first study injection at visit 4b. A HIV viral load sample is collected at visit 4b to time with the first injection(s).

1.3.2 Rationale for Cohort 1 and the related components of the study design

There is, to date, no clinical experience with use of oral CAB, CAB LA and RPV LA in children and adolescents less than 18 years of age. Oral RPV is approved for use as an antiretroviral medication in adolescents 12 years of age and older. Given this background, in Cohort 1 of the proposed study, CAB and RPV will first be studied separately to ascertain the dose and gather initial safety information for oral and injectable CAB (Cohort 1C) as well as injectable RPV following lead in with oral RPV (Cohort 1R). The initial age studied will be adolescents aged 12 to <18 years, and results from this group may inform the study details for a protocol amendment focusing on younger children. Cohort 1 study eligibility criteria require study participants to have demonstrated virologic suppression on a stable combination antiretroviral therapy regimen (cART), and this cART regimen is continued throughout the Cohort 1 study period to ensure continued virologic suppression. Enrollment into Cohort 1C versus Cohort 1R is determined by what cART regimen the participants have been receiving in order to avoid drug interactions (e.g. between RPV and boosted protease inhibitors) as well as duplication of study agent with another ARV from the same drug class. Hence, participants whose background cART contains a NNRTI or boosted PI will be enrolled in Cohort 1C and those on an INSTI based cART will be enrolled in Cohort 1R.
Safety, not PK, will primarily drive Cohort 1 enrollment and flow. As long as no safety concerns are noted, Cohort 1 enrollment will continue uninterrupted while an interim PK analysis is completed for the first 8 participants in Cohort 1C and Cohort 1R.

1.3.3 Rationale for Cohort 2 and the related components of the study design

The PK and initial safety data from Cohort 1 will support the opening of Cohort 2, where HIV-1 infected, virologically suppressed adolescents (including Cohort 1 participants meeting study eligibility criteria) will, stop their oral cART and switch to CAB plus RPV. Building on the experience from adult HIV-1 infected participants in LATTE 2 and the ATLAS study (ClinicalTrials.gov Identifier: NCT02951052), this study will use the same sequential approach of a 4 week (up to 6 week) oral lead in with both agents followed by a monthly injection of the LA formulation of both study agents.

Interim analyses will be performed after 8 participants have been enrolled into each Cohort 1C and Cohort 1R with separate analyses for each cohort. The partial PK and safety information (on one of two study products) of Cohort 1 participants, combined with the PK and safety interim analysis information for both study products from the initial cohort, is expected to support the cautious limited initial opening of Cohort 2 to participants from Cohort 1. General enrollment to Cohort 2 will only open after all subjects have been enrolled and followed up in Cohort 1. Cohort 1 participants who express interest and meet the Cohort 2 study eligibility criteria will be allowed to enroll into Cohort 2 after the interim analysis. The rationale for restricting Cohort 2 to Cohort 1 graduates until completion of Cohort 1 is based on safety. The Cohort 1 graduates will have completed the PK and safety assessments and will already have their own PK and safety profile data on one of the two study agents. This will allow those completing Cohort 1 to stop their cART and graduate to Cohort 2 whilst the remaining participants in Cohort 1 are enrolled.

The proposed single arm Cohort 2 component of the study design is consistent with, and responsive to, HIV pediatric regulatory guidance from the European Union and USA, which allow extrapolation of adult efficacy data. The week 24 safety assessment time point will serve as the primary endpoint for Cohort 2, but safety, acceptability, PK and antiviral efficacy will continue to be assessed through week 96 with related study endpoints at weeks 24, 48 and 96. These data will provide important information on the short term and long term, through 96 weeks use of this once a month, two-drug injectable ART in adolescents.

1.3.4 Rationale for Long-Term Safety and Washout PK Follow-up (LSFU)

As earlier mentioned, the CAB LA and RPV LA formulations have a pharmacokinetic decay rate which exposes the injected individual to detectable levels of CAB and RPV for up to 52 or more weeks after an injection. Given this prolonged decay rate, clinical protocols to date using these LA agents have included a long-term follow-up to assess safety and development of resistance or viral rebound in the setting of declining study product levels following the last intramuscular injection of either or both CAB LA and RPV LA. These assessments are confounded by the contributions of the oral cART these HIV-infected patients will receive after they stop the long-acting formulations. Any participant discontinuing the intramuscular injections (either as scheduled or earlier than scheduled), will then be followed per the 48-week follow-up visit schedule.
1.3.5 Rationale for acceptability and tolerability assessments including qualitative phone interviews: participants and parent/caregiver

Following enfuvirtide, an HIV fusion inhibitor, that was the first of a novel class of antiretroviral drugs proposed as twice a day subcutaneous injections as part of cART for the treatment of HIV-1 infection, the intramuscular LA formulations will be the first injectable antiretroviral agents to be studied in adolescents. Acceptability and tolerability will be critical to understand from both the standpoint of the participants and their caregivers, who facilitate their access to healthcare. Soliciting feedback on the LA formulations from diverse groups of patients and their caregivers will help inform ways to further optimize the delivery of these agents and their acceptability in future clinical trials as well as their offering as part of standard of care when these agents are approved. To accomplish this important study aim, assessments will be administered by site staff to participants via questions covering topics on participant perceptions of the study product injections, reasons for switching from daily oral cART to long-acting study products, satisfaction with treatment, and quality of life at multiple time points throughout the study. In addition, a single in-depth qualitative phone interview will be conducted with selected participants, and, separately, with selected parents or caregivers, to identify acceptability concerns unique to the participant population. The assessments are similar to ones that have been utilized for adult studies of LA agents, but have been adapted to be age-appropriate. These assessments will allow comparisons of adolescent feedback to that from adults. Some assessments such as the feedback from the caregivers will be unique to pediatric and adolescent populations and IMPAACT 2017 will provide the first opportunity to get this information.

1.3.6 Rationale for proposed doses of study agents

1.3.6.1 Oral CAB

Oral CAB has been administered to HIV infected adults at doses of 5mg to 60mg once daily. Currently, oral CAB 30mg once daily has been selected as the oral lead-in dose, administered for 4 weeks as a safety check prior to initiation of CAB LA in adults. CAB 30mg once daily in HIV infected adult subjects achieved a geometric mean $C_{\text{max}}$ and $C_{\text{t}}$ of 7.5$\mu$g/mL and 4.2$\mu$g/mL, respectively (LAI116482, LATTE, Table 1). A population model including data following administration of both oral CAB and CAB LA in healthy and HIV infected adults has been developed to select doses for further studies. No gender or BMI difference has been observed following administration of oral CAB. Data included in the model were from subjects ranging from 48 to 167kg. An allometric scaling term (power function of weight on $\text{CL/F}$ and $V$) was included to improve model fit such that CL/F and V decrease with decreasing weight, thereby increasing plasma concentrations. This same model was utilized to extrapolate exposures following oral CAB 30mg once daily down to 35kg individuals. Predicted steady state parameters following CAB 30mg once daily are summarized by weight group in Table 1. For adolescents weighing 35 to <50kg, oral CAB 30mg once daily is predicted to achieve median exposures that are ~30-40% higher than in adults but less than oral CAB 60mg once daily, which has been administered safely in HIV infected adult subjects for 96 weeks. For those weighing $\geq$50kg, oral CAB 30mg once daily is predicted to achieve median exposures that are ~10% higher than in adults and below oral CAB 60mg. Simulated steady state median (90% Prediction Interval: PI) concentration-time profiles over one dosing interval following CAB 30mg once daily are shown by weight band in Figure 8.

Based on modeled predictions, CAB 30mg once daily is expected to be safe in adolescents and has been selected as the initial oral lead-in dose for Cohort 1 of this study. Data following oral
administration of 30mg once daily will be reviewed for subjects participating in Cohort 1 of the study, and a decision may be made to alter/decrease the oral lead-in for use in Cohort 2 based on weight band of each participant. If a different oral dose is chosen, additional PK assessments will be performed in Cohort 1 before incorporating into Cohort 2.

Table 1. Predicted Steady State CAB Parameters following Oral CAB 30mg QD in Adolescents compared to Observed Adult Values

<table>
<thead>
<tr>
<th>Plasma CAB Parameter</th>
<th>Observed Adult Data (LAI116482, LATTE) Geometric Mean [95% CI] (range)</th>
<th>35 to &lt;50kg</th>
<th>≥50kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median (90% PI)</td>
<td>Peds:Adults Relative Exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vs 30mg</td>
<td>vs 60mg</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>2.8 [2.3, 3.3] (1.6-4.6)</td>
<td>7.5 [6.3, 8.9] (4.9-11)</td>
<td>12 [8.8, 15] (7.3-19)</td>
</tr>
<tr>
<td>CT (μg/mL)</td>
<td>1.4 [1.2, 1.5] (0.5-3.9)</td>
<td>4.2 [3.8, 4.7] (0.9-4.4)</td>
<td>7.9 [7.2, 8.8] (2.6-20)</td>
</tr>
<tr>
<td>AUC(0-τ) (μg•h/mL)</td>
<td>46 [38, 55] (28-85)</td>
<td>134 [110, 163] (79-208)</td>
<td>195 [138, 277] (103-334)</td>
</tr>
</tbody>
</table>
1.3.6.2 Injectable Cabotegravir

CAB LA has been administered intramuscularly to healthy and HIV infected adults at doses of 100mg to 800mg. In HIV-infected subjects, CAB LA has maintained virologic suppression on a maintenance dose of 400mg IM Q4W injections in conjunction with RPV LA (200056). The population PK model described above included IM data in 416 adults (12% female). Gender and BMI were significant covariates affecting the absorption rate constant following IM administration, such that absorption is slower in females than males and in subjects of larger BMI. These covariates were retained in the model extrapolating to smaller individuals expected to be enrolled in IMPAACT 2017 study. Weight and BMI were correlated for the purposes of the simulations. In adolescent subjects weighing 35 to <50kg, CAB LA 400mg IM Q4W is predicted to achieve median steady state trough concentrations that are ~20% higher than in adults but less than oral CAB 30mg once daily; for those weighing ≥50kg, CAB LA 400mg IM Q4W is predicted to achieve median steady state trough concentrations that are equivalent to adults (Table 2). Simulated median (90% PI) concentration-time profiles following CAB LA 600mg IM (Dose 1) then 400mg IM Q4W are shown by weight band in Figure 9. Greater than 95% of adolescents weighing 35 to <50kg are predicted to maintain concentrations above 4x PA-IC₉₀ throughout dosing; those ≥50kg are predicted to achieve concentrations >4x PA-IC₉₀ throughout dosing, with the exception of the first dosing interval, where ~90% are expected to exceed this target. The median CAB concentration 28 days (C28D) after the third injection is anticipated based on simulations to be within 10-15% of the true CAB C28D at steady-state value.

Based on this, CAB PO 30mg q.d. and CAB LA 600mg IM x 1 then 400mg IM Q4W are expected to be safe in adolescents and have been selected as the initial regimen for Cohort 1 of this study, which is the same as the adult CAB regimen in current Phase 3 studies. Pharmacokinetics and safety data following CAB PO and LA will be reviewed for subjects
participating in Cohort 1C of the study. A decision may be made based on PK and safety whether the initial Cohort 1C CAB PO and LA doses should move forward for use in Cohort 2 or whether an alternative dosing strategy is needed. While somewhat higher CAB plasma concentrations are expected in lower weight adolescent subjects, given the safety and tolerability seen in adults at the higher CAB PO dose of 60 mg daily and CAB LA dose of 800mg q 8 weeks, this study will be permissive to CAB exposures that are somewhat higher, as long as not associated with any safety concerns. If the initial CAB dosing in Cohort 1C fails to meet exposure criteria and modification of the CAB dosing strategy is needed, the new dosage will be studied in Cohort 1C with PK evaluations analyzed before being used in Cohort 2. See additional details in pharmacology plan outlined in Section 10.

**Table 2. Predicted Steady State CAB Parameters following CAB LA 400mg IM Q4W compared with Observed data in Adults**

<table>
<thead>
<tr>
<th>Plasma CAB Parameter</th>
<th>Observed Adult Data [GeoMean [95% CI] (range)]</th>
<th>Adolescent Weight Group</th>
<th>Relative Exposure</th>
<th>Relative Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30mg QD (LATTE)</td>
<td>400mg IM Q4W (LATTE-2)</td>
<td>Median (90% PI)</td>
<td>Vs 30mg Oral</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>7.5 [6.3, 8.9] (5-11)</td>
<td>3.5 [3.2, 3.8] (2.4, 11)</td>
<td>5.4 (2.4, 11)</td>
<td>0.72</td>
</tr>
<tr>
<td>Ct (µg/mL)</td>
<td>4.2 [3.8, 4.7] (0-9.4)</td>
<td>2.4 [2.2, 2.5] (0.8-6.7)</td>
<td>3.0 (1.1, 5.9)</td>
<td>0.71</td>
</tr>
</tbody>
</table>
1.3.6.3 Oral Rilpivirine (RPV)

RPV 25-mg once daily (oral tablet) is approved for the treatment of HIV-1 infection in ART-naïve patients 12 years of age and older in multiple countries including the USA, the EU, Canada, and Japan as EDURANT® and as part of ODEFSEY®. This approved dose of oral rilpivirine will be used as part of the oral lead-in in Cohort 1R and Cohort 2.

1.3.6.4 Injectable Rilpivirine

RPV LA (formulation G001) has been administered intramuscularly (IM) to healthy and HIV infected adults at doses of 300 mg to 1200 mg. In HIV-infected subjects, RPV LA maintained suppression of infection following monthly (Q4W) IM injections of 600 mg or bi-monthly (Q8W) injections of 900 mg, in conjunction with CAB LA monthly or bi-monthly (LATTE-2; 200056). Currently, a dosing regimen of a RPV LA 900 mg IM loading dose followed by Q4W IM injections of 600 mg, in conjunction with CAB LA Q4W, is being evaluated in two Phase 3 studies in adults (ATLAS [ClinicalTrials.gov Identifier: NCT02951052] and FLAIR [ClinicalTrials.gov Identifier: NCT02938520]).

A population PK model for RPV LA after IM administration was developed based on data in healthy and HIV-1 infected subjects. It comprises a 2-compartment PK model with a first-order disposition from the central compartment. The absorption part of the PK profile is described by a parallel pathway consisting of a direct first-order absorption from the depot compartment (KA1) and an indirect first-order absorption via a second intermediate compartment into the central compartment (KA2). Based on the currently available data in adults (bodyweight range 48 to 140 kg), no significant covariates (including BMI, bodyweight or gender) were identified for the
population PK model of RPV LA. In order to assess what could occur in case bodyweight would become more important for the absorption of RPV LA in adolescents, a conservative approach using a standard allometric scaling term for absorption rate was used (Table 3). The impact of making the absorption rate a function of bodyweight however had minimal effects on Cmax or Ctrough (C28D) values. Even with this added scaling factor, in adolescent subjects weighing 35 to <50kg or ≥50kg, a RPV LA regimen of 600mg IM Q4W (after loading dose of 900 mg IM) is predicted to achieve median steady state trough concentrations that are similar to those in adults with the same RPV LA regimen or those with oral RPV 25mg once daily (ratio’s very close to 1, Table 4). In Cohort 1R, three injections of RPV LA will be given. The median RPV C28D after the third injection is anticipated to be < 30% lower than the RPV C28D at full steady-state.

Table 3. Predicted Steady State RPV PK Parameters following RPV LA 600mg IM Q4W compared with Predicted data for oral RPV and RPV LA Q4W in Adults

| Plasma RPV Parameter | Predicted* RPV LA Data in Adolescents | 35 to <50kg | ≥50kg |
|----------------------|----------------------------------------|-------------|
|                      | Relative Exposure                      | Median (90% PI) | Vs 25mg Oral a | Vs adults 600mg IM b | Median (90% PI) | Vs 25mg Oral a | Vs adults 600mg IM b |
| C<sub>max</sub> (ng/mL) | 134 (75.3, 243) | 0.99 | 1.02 | 131 (74, 235) | 0.97 | 0.99 |
| C<sub>t</sub> (ng/mL) | 89 (46.4, 1174) | 1.19 | 0.99 | 88 (45, 171) | 1.18 | 0.98 |

*a using model with scaling factor on Ka for adolescents

Based on this, RPV LA 900mg IM x 1 (loading dose) then 600mg IM Q4W is expected to be safe in adolescents, even when taking into account a scaling factor for Ka, and has been selected as the initial regimen for Cohort 1R of this study. Data following RPV LA will be reviewed for subjects participating in Cohort 1R of the study, and a decision may be made to alter/decrease the maintenance dose, which will be studied in Cohort 1R before incorporating into Cohort 2.

Table 4. Comparison of Predicted Median (90% PI) Trough following 3rd IM dose given every 4 weeks versus at steady state in adolescents 35 kg and above

<table>
<thead>
<tr>
<th>Plasma Parameter</th>
<th>After 3&lt;sup&gt;rd&lt;/sup&gt; Dose</th>
<th>Steady State (SS)</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Dose/SS Trough Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB C&lt;sub&gt;t&lt;/sub&gt; (μg/mL)</td>
<td>2.73 (0.93, 5.82)</td>
<td>3.0 (1.1, 5.93)</td>
<td>91%</td>
</tr>
<tr>
<td>RPV C&lt;sub&gt;t&lt;/sub&gt; (ng/mL)</td>
<td>64 (31, 119)</td>
<td>89 (46, 173)</td>
<td>72%</td>
</tr>
</tbody>
</table>
1.4 Risk/Benefit Assessment

1.4.1 Cohort 1

Cohort 1 participants will remain on the same cART regimen on which they have a previous history of sustained HIV virologic suppression throughout Cohort 1 participation. Additionally, assignment to Cohort 1C or Cohort 1R is based on their cART composition such that there are no drug interactions with study agents and avoiding redundancy of agents from the same class of antiretrovirals. Given all of this there is no anticipated risk of loss of HIV virologic control specifically related to participation in Cohort 1.

Oral rilpivirine is currently approved for use in HIV-infected patients 12 years and older and the side effect profile has been well described and outlined in the package insert. The safety profile of oral cabotegravir, CAB LA and RPV LA is summarized earlier in this section and detailed in the related investigator’s brochures. In order to maximally identify any acute toxicity prior to administration of a non-dialyzable, non-removable depot injection of the CAB LA and RPV LA that have a slow pharmacokinetic decay, a 4-6 week lead-in period of daily oral (short acting) CAB or RPV is planned. By enrolling patients with a history of sustained virologic suppression on cART and maintaining this cART backbone throughout Cohort 1 follow-up, the likelihood of virologic failure and associated development of resistance to study agents is highly unlikely.

Injection site reactions reported to date have been relatively common but not significant, becoming less frequent over time, and not life threatening nor serious. Despite ISRs, there has been high acceptability of the long acting study agents amongst the adult study participants.

Other than a potential for an improved understanding of, and engagement in, HIV care both from the standpoint of the patient and their caregiver through participating in a safety, PK and acceptability/tolerability study of novel antiretroviral study agents and interacting with study staff, there is no immediate benefit to participation in Cohort 1. However, there is the potential of early access of Cohort 1 participants to Cohort 2 and its related risk-benefits. Based on the results of the interim PK and safety analysis of Cohort 1, graduates of Cohort 1 are likely, as per the study design, to have earlier access to enrollment into Cohort 2 and with that an opportunity to stop oral cART and switch to an entirely IM LA regimen.

1.4.2 Cohort 2

In addition to the study agent specific side effects, Cohort 2 participants run the risk of having loss of virologic suppression, and the potential development of resistance mutations, once switched off oral cART to the two study agents, first as daily oral therapy and followed by once a month injections of the long-acting formulations. There is a growing body of evidence assessing the efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy in HIV-infected patients. A systematic review and meta-analysis on this topic concluded as a switch strategy, dual therapy was equally efficacious to standard cART and although the dual therapy tended to have lower rates of adverse events than standard cART be it in an initial treatment setting or a switch strategy, it was associated with a higher relative risk of selecting virus with drug resistance mutations at virological failure (6). The overall assessment of this anticipated risk of development of resistance in cohort 2 of IMPAACT 2017 is judged to be low for several reasons. LATTE 2 results to date in previously treatment-naïve HIV-infected adults show that the CAB LA plus RPV LA regimen is well tolerated, demonstrates
durable virologic response and the rate of treatment emergent resistance is extremely low through week 96 (9). Secondly, the dose of study agents confirmed from Cohort 1 PK is likely to be comparable to that which has currently been shown to be efficacious in adults. Lastly, only patients with durable virologic suppression are enrolled in Cohort 2 and, in addition with an injectable only regimen for majority of the study period, will get directly observed therapy making the likelihood of unobserved poor adherence to medications much less likely.

The potential benefit of participating in Cohort 2 relates to the convenience of not having to take daily oral cART and avoiding any oral cART related toxicities, medication fatigue and adherence issues. Long-acting two class therapy consisting of CAB LA + RPV LA as an IM regimen has the benefit of being a NRTI-sparing regimen for long-term treatment of HIV infection which will avoid known NRTI-associated adverse drug reactions and long-term toxicities. Additionally, a two-drug combination therapy with CAB LA plus RPV LA may offer a better tolerability and resistance profile, as well as improved adherence and treatment satisfaction in virologically suppressed participants improving the quality of life for patients with living with HIV.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with CAB LA and RPV LA, and the study as a whole, are justified by the anticipated benefits that may be afforded to treatment-experienced patients with HIV-1 infection.

1.5 Hypotheses

Cohort 1: CAB (oral and IM) and RPV (IM) 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 IM and RPV IM, when given as dual therapy, to stable, virologically suppressed adolescents will be safe through week 24 in HIV-infected adolescents at the selected dose.

2 OBJECTIVES

2.1 Primary Objective: Cohort 1 (continuing a background cART regimen)

The primary objective of this study is:

2.1.1 To confirm the doses for oral CAB followed by injectable CAB LA in HIV-infected, virologically suppressed adolescents by evaluating:

2.1.1.1 Safety and multiple dose PK of oral CAB through Week 4;

2.1.1.2 Safety and multiple dose PK of CAB LA through Week 16.

2.1.2 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.
2.2 Primary Objective: Cohort 2 (discontinuing a background cART regimen)

The primary objective of this study is:

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

2.3 Secondary Objectives: Cohort 1

The secondary objectives of this study are:

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

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

2.4 Secondary Objectives: Cohort 2

The secondary objectives of this study are:

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

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

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

2.5 Other Objectives

The other objectives of this study are:

2.5.1 To evaluate the tolerability and acceptability of CAB LA + RPV LA through Week 24, through Week 48, and through Week 96 in HIV-infected, virologically suppressed adolescents (Cohort 2).

2.5.2 To evaluate the safety, antiviral and immunologic activity, and characterize PK of CAB LA + RPV LA through Week 96 in HIV-infected, virologically suppressed adolescents (Cohort 2).

2.5.3 To evaluate adolescent participant’s experience of CAB LA and/or RPV LA, and parent/caregiver’s experience and perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA (Cohort 1 and Cohort 2).

2.5.4 To evaluate the tolerability and acceptability, and characterize long-term safety and PK through 48 weeks following permanent discontinuation of CAB LA or RPV LA (Cohort 1).
2.5.5 To evaluate the tolerability and acceptability, and characterize long-term safety and PK through 48 weeks following permanent discontinuation of CAB LA + RPV LA (Cohort 2).

2.5.6 To describe HIV-1 resistance in participants experiencing virologic failure (Cohort 1 and Cohort 2).

3 STUDY DESIGN

This is a Phase I/II, multi-center, open-label, non-comparative study to confirm the dose and evaluate the safety, tolerability, acceptability, and PK of oral CAB, long-acting injectable CAB (CAB LA), and long-acting injectable RPV (RPV LA) among up to 155 virologically suppressed HIV-1 infected children and adolescents aged 12 to <18 years.

Up to 60 parents/caregivers of adolescent participants will also be enrolled to take part in in-depth qualitative interviews. Unless otherwise noted, the term ‘participant’ will refer to the adolescent participants.

The study design includes 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. 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. Any female participant who permanently discontinues study product (either oral or injectable study product) due to pregnancy will also be followed per the LSFU visit schedule, based on the date of the positive confirmatory pregnancy test result, for an additional 48 weeks. Expectations regarding the LSFU visit schedule for specific participants are described in further detail in Sections 3.3 and 6.5.

The study will open to accrual in Cohort 1, in which participants, in addition to continuing their pre-study cART regimen, will receive either oral CAB or oral RPV (Step 1) followed by either CAB LA or RPV LA (Step 2). Cohort 1 participants will be assigned either CAB (Cohort 1C) or RPV (Cohort 1R) based on their pre-study cART regimen. An interim analysis of safety and PK data will be performed (as described in Sections 9 and 10) following the first eight evaluable Cohort 1C and the first eight evaluable Cohort 1R participants completing their Cohort 1, Step 2 Week 16 study visit. Cohort 2 will initially open to accrual based on these interim analyses; however, accrual at this stage will be limited to Cohort 1 participants who meet criteria to enter Cohort 2. Once Cohort 1 is fully enrolled (i.e. 20 Cohort 1C evaluable, and 15 Cohort 1R evaluable) and a full cohort data analysis is performed, accrual into Cohort 2 will be opened to additional participants who were not previously enrolled in Cohort 1. Upon Cohort 2 Entry (i.e. Cohort 2, Step 3), all Cohort 2 participants will discontinue their pre-study cART regimen and receive both study products — CAB and RPV — at the doses confirmed in Cohort 1.

Safety and PK evaluations will be performed in each cohort, as well as during LSFU. Antiviral activity assessments will be performed in each cohort, although primarily in Cohort 2. Acceptability and tolerability will be assessed in each cohort and during LSFU, with all
participants completing quantitative questionnaires and a sub-set of participants completing in-depth qualitative interviews.

Further information describing the two cohorts is provided in Sections 3.1 and 3.2. Further information describing the LSFU visit schedule, for both Cohort 1 and Cohort 2 participants, is provided in Section 3.3. Refer to Figure 1, Figure 2, Figure 3, and Figure 4 for an overview of Cohort 1, Cohort 2, and the overall study design for the adolescent participants; Section 4 for the eligibility criteria relevant to each cohort and step; and Section 6 and Appendix I for the study visit and procedure schedules for each cohort. Details regarding the in-depth qualitative interviews are provided in Section 11.

Parent/caregiver eligibility criteria are provided in Section 4, with further details regarding the parent/caregiver in-depth qualitative interviews in Appendix V-A.

3.1 Cohort 1

Up to 55 participants will be enrolled in Cohort 1 to achieve a minimum of 35 evaluable (refer to Section 9.1 for the definition of evaluable for this cohort). Within this cohort, participants will be assigned to either Cohort 1C (n = 20 evaluable), in which participants will receive CAB, or Cohort 1R, in which participants will receive RPV (n = 15 evaluable). Assignment to Cohort 1C or 1R will be based on each participant’s pre-study cART regimen:

- Participants on a PI-based and/or NNRTI-based cART regimen will be assigned to Cohort 1C
- Participants on an INSTI-based cART regimen will be assigned to Cohort 1R

All participants in Cohort 1 will remain on their pre-study cART regimen and will additionally receive either CAB (Cohort 1C) or RPV (Cohort 1R).

Upon enrollment, Cohort 1 participants will receive oral CAB (Cohort 1C) or oral RPV (Cohort 1R) for at least 4 weeks (and up to 6 weeks) in Step 1. An intensive PK visit will be conducted at the Week 2 visit and over a 24-hour period. Data collected through the Week 4a study visit will be assessed to determine eligibility for each participant to enter Step 2 and receive injectable CAB LA or RPV LA, respectively. The Cohort 1 Week 4b visit serves as the Step 2 Entry visit. This visit should be scheduled to occur as soon as possible after Week 4a laboratory test results are available, to minimize the time between the Week 4a visit and initiation of the injectable study products in Step 2. Clinical assessments conducted at the Week 4b visit, and prior to administering the first injection, will also be used to confirm Step 2 eligibility.

Cohort 1 participants who meet eligibility criteria for Step 2 will receive their last oral dose of CAB or RPV on the same day as their first injection of CAB LA or RPV LA, at the Week 4b Step 2 Entry visit. See Section 4.3 for eligibility criteria to enter Step 2. 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 every four weeks over an eight-week period, specifically at the Week 4b (Step 2 Entry), Week 8, and Week 12 visits. Cohort 1 Step 2 participants will be followed for safety and PK assessments through their Week 16 visit.
In Step 2, Weeks 5 through 16 visits will be scheduled based on the date of which the first injection is administered (Week 4b Step 2 Entry visit). Cohort 1 Step 2 participants will be followed for up to an additional 48 weeks, per the LSFU visit schedule, upon premature injectable study product discontinuation or upon completion of the Step 2 Week 16 visit. Cohort 1 participants who have completed all Step 2 visits may enroll to Cohort 2 (if eligible), prior to completing all LSFU visits. Further guidance on scheduling study visits are provided in the IMPAACT 2017 Manual of Procedures (MOP).

Once eight evaluable Cohort 1C participants and eight 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 (i.e. four weeks after the last study product injection at the Week 12 study visit), an interim analysis will be performed to:

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

Refer to Section 9 for a detailed description of the interim Cohort 1 analysis and associated decision-making. Accrual into Cohort 1 will continue while this analysis is performed.

After the interim analysis and once 20 evaluable Cohort 1C participants and 15 evaluable Cohort 1R participants have enrolled, an analysis of safety and PK evaluations will be performed to determine whether criteria have been sufficiently met to fully open Cohort 2 to accrual, including accrual of participants who were not previously enrolled in Cohort 1.

Once 20 evaluable Cohort 1C participants and 15 evaluable Cohort 1R participants have completed the injectable study product dosing in Step 2, and have completed safety and PK evaluations through the Cohort 1 Step 2 Week 16 visit (i.e., four weeks after the last injection), an analysis of all Cohort 1 safety and PK data will be performed to:

- Confirm the dose of the oral and injectable CAB study products, and the injectable RPV study product to be provided in Cohort 2

Refer to Section 9 for a detailed description of the full Cohort 1 analysis and associated decision-making.

Participant safety will be monitored throughout follow-up, and samples for antiviral activity and PK evaluations will be collected at visits as specified in Section 6, with blood volume ranges provided in Appendix I-A. Acceptability and tolerability will be assessed with all participants completing quantitative questionnaires, and a sub-set of participants also completing in-depth qualitative interviews.

3.2 Cohort 2

Up to 155 participants may participate in Cohort 2: Up to 100 participants, who have not previously participated in Cohort 1, will be enrolled directly into Cohort 2 to achieve approximately 70 evaluable adolescents newly enrolling to the study.
In addition to the up to 100 participants enrolling directly into Cohort 2, adolescents who participated in Cohort 1 Step 2 (up to 55 participants) may continue study participation in Cohort 2 Step 3, if eligible. These participants may screen and enroll into Cohort 2 either prior to completing all scheduled LSFU study visits, or resume study participation if after having already exited the study. See Section 6.2 for additional considerations regarding Cohort 1 Step 2 participants screening and enrolling into Cohort 2 Step 3.

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. A PK visit will be conducted at the Week 2 visit. Data collected through the Week 4a study visit will be assessed to determine eligibility for each participant to enter Step 4 and receive injectable CAB LA + RPV LA. The Cohort 2 Week 4b visit serves as the Step 4 Entry visit. This visit should be scheduled to occur as soon as possible after Week 4a laboratory test results are available, to minimize the time between the Week 4a visit and initiation of the injectable study products in Step 4. Clinical assessments conducted at the Week 4b visit, and prior to administering the first injection, will also be used to confirm Step 4 eligibility.

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. See Section 4.4 for eligibility criteria to enter Step 4. Cohort 2 participants who do not meet eligibility criteria for Step 4 will discontinue use of oral CAB+RPV and exit the study 28 days after their last oral study product dosing. Cohort 1 Step 2 participants who continue in Cohort 2 Step 3, but are not eligible to progress to Cohort 2 Step 4, will be followed per the LSFU visit schedule.

In Step 4, participants will receive injectable CAB LA + RPV LA. Two IM injections, a single injection of CAB LA and a single injection of RPV LA, will be administered beginning at the Week 4b (Step 4 Entry) visit and continuing every four weeks thereafter, over a 92-week period, until the Week 96 visit. Study visits during Step 4 will be scheduled based on the date of which the first CAB LA + RPV LA injections were administered (Week 4b Step 4 Entry). Upon premature injectable study product discontinuation, Cohort 2 Step 4 participants will be followed for 48 weeks per the LSFU visit schedule. Further guidance on scheduling study visits are provided in Section 6.1 and the IMPAACT 2017 MOP.

At the Week 96 visit, Cohort 2 Step 4 participants may choose to continue to receive injectable CAB LA + RPV LA external to the protocol, and will exit the study. See Section 14.11 for more information regarding post-trial access to study products. Participants who choose to 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.

Participant safety will be monitored, and samples for antiviral activity and PK evaluations will be collected, at visits as specified in Section 6; blood volume ranges are provided in Appendix I-B. Acceptability and tolerability will be assessed with all participants completing quantitative questionnaires, and a subset of participants also completing in-depth qualitative interviews.

### 3.3 Long-term Safety and Washout PK Follow-up (LSFU)

Specified participants will be followed for an additional 48 weeks to assess long-term safety and washout PK of the study products. Participants may enter into the LSFU visit schedule at different timepoints:

- Premature permanent discontinuation of injectable study product during Step 2 or Step 4
• Completion of the Cohort 1 Step 2 Week 16 visit
• Completion of the Cohort 2 Step 4 Week 96 study visit but choosing to not continue to receive injectable CAB LA + RPV LA external to the protocol
• Female participants who discontinue study product use (either oral or injectable study product) due to pregnancy during Steps 1-4

See Section 6.5 and Appendix I-C for detailed visit procedures. All Cohort 2 participants will resume (non-study provided) oral cART as soon as possible, and within 4 weeks of discontinuing study product. See Section 8.8 for criteria for premature permanent discontinuation of study product.

Participants permanently discontinuing injectable study product use will be followed for an additional 48 weeks after their last study product injection. LSFU visits will be scheduled approximately 4, 12, 24, 36, and 48 weeks after the last injection, after which participants will exit the study. Additionally, for Cohort 1 Step 2 participants who complete their Week 16 visit, their next scheduled visit will be the LSFU Week 12 Visit (i.e. their LSFU 4 Weeks Visit is skipped). Cohort 1 Step 2 participants who enroll to Cohort 2 Step 3, but are then not eligible to progress to Cohort 2 Step 4 will be followed per the LSFU visit schedule, also based on the date of their last study product injection (i.e. their Cohort 1 Step 2 Week 12 visit).

At the Week 96 visit, Cohort 2, Step 4 participants choosing to discontinue receiving injectable CAB LA + RPV LA (external to the protocol) will be followed per the LSFU visit schedule. All Cohort 2, Step 4 participants following the LSFU visit schedule will complete all LSFU study visits, including the LSFU Week 4 study visit.

Female participants who permanently discontinue study product use (either oral or injectable study product) due to pregnancy during Steps 1-4 will be followed for an additional 48 weeks based on their confirmed positive pregnancy test result, per the LSFU visit schedule. For female participants who become pregnant during LSFU visits, the LSFU visits will continue as scheduled and not restart. Further details on participant management of contraception and pregnancy is located in Sections 6.13 and 8.3.

Participant safety will be monitored, and samples for antiviral activity and PK will be collected, at visits as specified in Section 6; blood volume ranges are provided in Appendix I-B. Acceptability and tolerability will be assessed with all participants completing quantitative questionnaires.

4 STUDY POPULATION

This study will be conducted among approximately 155 HIV-infected adolescents, and up to 60 parents/caregivers of study participants. Inclusion and exclusion criteria for each of the study populations are provided in Sections 4.1-4.5 below.

Adolescents will be enrolled into either Cohort 1 Step 1 or Cohort 2 Step 3. Adolescents who previously participated in Cohort 1 Step 2 and are continuing study participation by enrolling into Cohort 2, must meet the same eligibility criteria as other participants enrolling directly into Cohort 2 Step 3, unless otherwise noted.
The study-specific approach to recruitment, screening, and enrollment is described in Section 4.7. Considerations related to participant retention and withdrawal/termination from the study are provided in Sections 4.8 and 8.8, respectively.

4.1 Inclusion Criteria: Cohort 1 Step 1 and Cohort 2 Step 3

All the following criteria must be met for inclusion of any adolescent participant in Step 1 of Cohort 1, or in Step 3 of Cohort 2, unless otherwise noted:

4.1.1 At enrollment, 12 to < 18 years of age

*Note:* For Cohort 1 Step 2 participants, age will not be exclusionary for enrollment into Cohort 2 Step 3, if otherwise eligible.

4.1.2 *If not of legal age or otherwise not able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures:* Parent or legal guardian is willing and able to provide written informed consent for study participation and potential participant is willing and able to provide written assent for study participation

*If of legal age or otherwise able to provide independent informed consent as determined by site SOPs and consistent with site IRB/EC policies and procedures:* Willing and able to provide written informed consent for study participation

4.1.3 At enrollment, body weight ≥ 35 kg (77 lbs)

*Note:* For Cohort 1 Step 2 participants, body weight will not be exclusionary for enrollment into Cohort 2 Step 3, if otherwise eligible.

4.1.4 For Cohort 1, at enrollment, body mass index (BMI) ≤ 31.5 kg/m²

4.1.5 At enrollment, willing and able to comply with the study visit schedule and other study requirements, as determined by the site investigator or designee

4.1.6 Confirmed HIV-1-infection based on documented testing of two samples collected at different time points:

Sample #1 may be tested using any of the following:
- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One enzyme immunoassay (EIA) OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA polymerase chain reaction (PCR)
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test
Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

All samples tested must be whole blood, serum, or plasma. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified (US sites) laboratory. For tests performed in other (non-GCLP-compliant) settings, adequate source documentation including the date of specimen collection, date of testing, name of test/assay performed, and test result must be available.

4.1.7 For at least 6 consecutive months (defined as 180 consecutive days) prior to screening, and prior to enrollment, has been on stable cART consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs, as determined by the site IoR or designee, and based on participant or parent/guardian report and/or available medical records.

Note: Participants undergoing dose modifications to their antiretroviral regimen for growth or who are switching medication formulation(s) are considered to be on a stable cART.

4.1.8 Has at least one documented plasma HIV-1 RNA < 50 copies/mL from a specimen collected 6 to 12 months (defined as 180 to 365 days) prior to screening.

4.1.9 Has at least one documented plasma HIV-1 RNA < 50 copies/mL from a specimen collected within 6 months (defined as within 179 days) prior to screening.

4.1.10 At screening, has Grade 2 or lower of all the following laboratory test results:
- ALT (u/l)
- Lipase (u/l)
- Estimated creatinine clearance (CrCl; Schwartz formula mL/min/1.73m²)
- Platelets (cells/mm³)
- Hemoglobin (g/dL)

See Section 7.3.3 for guidance on severity grading. Laboratory tests may be repeated during the study screening period, with the latest result used for eligibility determination.

4.1.11 For participants enrolling into Cohort 1, Step 1 and on an atazanavir-containing (ATV) cART regimen, at screening, has total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin

4.1.12 At screening, has documented plasma HIV-1 RNA < 50 copies/mL.
4.1.13 At screening, QTc interval (automated machine readout or calculated using either Bazett or Fredericia) ≤ 500 msec

4.1.14 For females, has a negative hCG laboratory test result at entry

4.1.15 For females of childbearing potential, at entry, currently using at least one allowable effective method of contraception, and agrees to use at least one allowable effective method of contraception throughout study participation, for at least 30 days after discontinuation of oral study product, and for at least 48 weeks after discontinuation of CAB LA and/or RPV LA, and intending to delay any planned pregnancies until 30 days after last oral study product use or until 48 weeks after last injectable study product use.

*Note: See Section 6.13 for details regarding contraceptive counseling, a list of the allowed effective contraceptive methods for this study, and the definition of a female of childbearing potential. Hormonal-based contraceptives must have been initiated within the prescribed time, per the respective contraceptive method, to be considered effective at the time of Entry. The site IoR or designee is responsible for ensuring that the contraceptive is used in accordance with the approved product label, and counseling participants on proper use of chosen methods of contraception, including barrier methods.*

4.1.16 For Cohort 1 participants enrolling to Cohort 2, have completed all scheduled study visits in Cohort 1 Step 2

4.2 Exclusion Criteria: Cohort 1 Step 1, or Cohort 2 Step 3

Adolescents will be excluded from the study if any of the following are identified during the screening period:

4.2.1 Within 6 months (defined as within 179 days) prior to screening, two consecutive documented HIV-1 RNA values ≥50 copies/mL

*Note: Unconfirmed virologic HIV-1 RNA value of ≥ 50 copies/mL (transient detectable viremia, or “blip”) prior to screening is not exclusionary.*

4.2.2 For Cohort 1 participants enrolling to Cohort 2, Step 3, occurrence of any Grade 3 or higher adverse event assessed as related to study product during participation in Cohort 1 (including any long-term safety and washout PK follow-up visits).

4.2.3 For participants enrolling to Cohort 1 Step 1, based on available medical records, currently on either a cART regimen containing both a PI and an INSTI, or a cART regimen containing both an INSTI and a NNRTI.

4.2.4 As determined by the IoR or designee, and based on available medical records, known or suspected resistance to RPV

4.2.5 As determined by the IoR or designee based on available medical records, known or suspected resistance to INSTIs

4.2.6 History of congestive heart failure, symptomatic arrhythmia, or any clinically significant cardiac disease, as determined by the IoR or designee based on available medical records
4.2.7 At entry, known active tuberculosis infection, as determined by the IoR or designee based on available medical records

4.2.8 Known hepatitis B or hepatitis C infection, as determined by the IoR or designee based on available medical records

4.2.9 Clinically significant hepatic disease, as determined by the IoR or designee based on available medical records

4.2.10 Current or anticipated need for chronic anti-coagulation, as determined by the IoR or designee, based on available medical records

4.2.11 History of sensitivity to heparin or heparin-induced thrombocytopenia, as determined by the IoR or designee, based on available medical records

4.2.12 History of known or suspected bleeding disorder including history of prolonged bleeding, as determined by the IoR or designee, based on available medical records

4.2.13 Known or suspected allergy to study product components

4.2.14 More than one seizure within one year (defined as within 365 days) prior to entry, or unstable or poorly controlled seizure disorder, as determined by the IoR or designee, based on available medical records.

4.2.15 At entry, participant is receiving (or has received in the last 7 days) any disallowed medication listed in Section 5.7.

4.2.16 Current inflammatory skin condition that compromises the safety of intramuscular injections as determined by the IoR or designee.

4.2.17 Has a tattoo or other dermatological condition overlying the buttock region which, in the opinion of the IoR or designee, may interfere with interpretation of injection site reactions

4.2.18 Surgically-placed, or planned, buttock implants, per self-report

4.2.19 For females, lactating (per self-report and/or parent/guardian report) at entry

4.2.20 Enrolled in another clinical trial of an investigational agent, device, or vaccine

4.2.21 Any other condition or social circumstance situation that, in the opinion of the IoR or designee, would make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

4.3 Inclusion/Exclusion Criteria, Step 2 (Cohort 1 Progression Criteria, Step 1 to Step 2)

Cohort 1 Step 1 participants will be assessed for eligibility to progress from the oral lead-in phase (Step 1) to the injection phase (Step 2) primarily based on the safety assessments from the Cohort 1 Step 1 Week 4a study visit. Clinical assessments conducted prior to administering the first injection at the Week 4b visit will also be used to confirm eligibility to receive the injectable
study product. See Sections 6.3.3 and 6.3.4 for Week 4a and Week 4b visit scheduling, order of procedures, and visit windows, respectively.

All of the following criteria must be met in order for participants to be included in Cohort 1 Step 2:

4.3.1 Currently enrolled in Cohort 1, Step 1

4.3.2 At Cohort 1 Step 1 Week 4a study visit, or from confirmatory repeat testing of Cohort 1 Step 1 Week 4a study visit laboratory tests, has Grade 2 or lower of all the following laboratory test results:
- ALT (u/l)
- Lipase (u/l)
- Estimated creatinine clearance (CrCl; Schwartz formula mL/min/1.73m²)
- Platelets (cells/mm³)
- Hemoglobin (g/dL)

Note: For a Grade 2 ALT test result from this visit, refer to Section 8.1.5 for required participant management. Abnormal laboratory test result values from the Week 4a visit may be repeated within the target visit window, and if confirmatory testing results in Grade 2 or lower, the participant may be eligible to continue onto the injection phase, should all other eligibility criteria be met.

4.3.3 For females, at Cohort 1 Step 1 Week 4b study visit, has a negative hCG laboratory test result

4.3.4 Assessed by the IoR or designee as sufficiently adherent in Step 1 to permit an adequate evaluation of safety and tolerability as part of the oral lead-in phase prior to entry into the injection phase

Participants who meet any of the following criteria will be excluded from Cohort 1 Step 2:

4.3.5 Has permanently discontinued oral study product

4.3.6 Occurrence of any grade 3 or higher adverse event assessed as related to study product during participation in Step 1

4.3.7 Any other condition or social circumstance that, in the opinion of the IoR or designee, would make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.4 Inclusion/Exclusion Criteria, Step 4 (Cohort 2 Progression Criteria, Step 3 to Step 4)

Cohort 2 Step 3 participants will be assessed for eligibility to progress from the oral lead-in phase (Step 3) to the injection phase (Step 4) primarily based on the safety assessments from the Cohort 2 Step 3 Week 4a study visit. Clinical assessments conducted prior to administering the first injection at the Week 4b visit will also be used to confirm eligibility to receive the injectable study product. See Sections 6.4.3 and 6.4.4 for Week 4a and Week 4b visit scheduling, order of procedures, and target visit windows, respectively.
All of the following criteria must be met in order for participants to be included in Cohort 2 Step 4:

4.4.1 Currently enrolled in Cohort 2, Step 3

4.4.2 At Cohort 2 Step 3 Week 4a study visit, or from confirmatory repeat testing of Cohort 2 Step 3 Week 4a study visit laboratory tests, has Grade 2 or lower of the following laboratory test results:
   • ALT (u/l)
   • Lipase (u/l)
   • Estimated creatinine clearance (CrCl; Schwartz formula mL/min/1.73m²)
   • Platelets (cells/mm³)
   • Hemoglobin (g/dL)

*Note: For a Grade 2 ALT test result from this visit, refer to Section 8.1.5 for required participant management. Abnormal laboratory test result values from the Week 4a visit may be repeated, within the target visit window, and if confirmatory testing results in Grade 2 or lower, the participant may be eligible to continue onto the injection phase, should all other eligibility criteria be met.*

4.4.3 For females, at Cohort 2 Step 3 Week 4b study visit, has a negative hCG laboratory test result

4.4.4 Assessed by the IoR or designee as sufficiently adherent in Step 3 to permit an adequate evaluation of safety and tolerability as part of the oral lead-in phase prior to entry into the injection phase

Participants who meet any of the following criteria will be excluded from Cohort 2 Step 4:

4.4.5 Has permanently discontinued oral study products

4.4.6 Occurrence of any grade 3 or higher adverse event assessed as related to study product during participation in Cohort 2, Step 3

4.4.7 Any other condition or social circumstance that, in the opinion of the IoR or designee, would make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.5 Inclusion/Exclusion Criteria: Parents/Caregivers

Selected parents or caregivers of adolescents may be enrolled to complete qualitative phone interviews. See Appendix V-A for more information regarding the selection process, and coordination of scheduling the interviews. All of the following criteria must be met for the parent/caregiver to be enrolled:

4.5.1 Selected by the protocol team for participation in the study

4.5.2 Willing and able to provide informed (verbal or written) consent for study participation
4.5.3 Per the adolescent participant, has knowledge of how the adolescent participant tolerated the study product, and lives with or has regular supportive contact with the adolescent participant.

4.5.4 Per parent/caregiver self-report, has knowledge of how the participant tolerated the study product, and lives with or has regular supportive contact with the adolescent participant.

4.5.5 Willing and able to complete interview in English by phone.

Parents and/or caregivers of participants who meet the following criterion will be excluded from study participation:

4.5.6 Any condition or social circumstance that, in the opinion of the IoR or designee, would make study participation unsafe for either the parent/caregiver or the adolescent participant, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.6 Co-Enrollment Considerations

Co-enrollment in observational or other studies not involving an investigational agent, device, or vaccine may be permitted although careful consideration must be given to visit burden, blood draw volumes, and interpretation of outcome data across studies. Requests for co-enrollment must be approved in advance by both study teams. Requests for such approval or questions related to co-enrollment should be emailed to the IMPAACT 2017 Clinical Management Committee (CMC).

4.7 Recruitment, Screening, and Enrollment Process

This section provides a description of the recruitment methods, screening and enrollment processes, and the definition of enrollment for the adolescent participants.

See Appendix V-A for recruitment, eligibility confirmation, and enrollment processes, including the definition of enrollment, for parents/caregivers to take part in a single qualitative phone interview.

4.7.1 Recruitment and Screening of Cohort 1 (Step 1) and Cohort 2 (Step 3) Participants

Recruitment methods for this study may vary across sites. All participants must be 12 to less than 18 years of age at the time of enrollment (with the exception of adolescents who previously participated in Cohort 1 Step 2 and continuing into Cohort 2, as noted in Section 4.1.1 above). Recruitment of participants, for both Cohort 1 and Cohort 2, is expected to rely on current patients being seen at a study clinic or from active identification and referral of HIV-1-infected children and adolescents who are ART-experienced and virologically suppressed; participants may be perinatally or behaviorally infected.

Any advertising materials must undergo approval by each participating site’s institutional review board (IRB)/Ethics Committee (EC). Sites are encouraged to solicit input and feedback on recruitment materials from their local Community Advisory Board, particularly any adolescent Community Advisory Board members.
Upon identification of a potentially eligible participant, study staff will provide information about the study to the parent or guardian and/or the potential participant (as applicable). Each parent or guardian and/or potential participant (as applicable) who expresses interest in learning more about the study will be provided additional information, education, and counseling as part of the study informed consent process. The process will include detailed review of the study informed consent and assent forms (as applicable), time to address any questions or concerns the potential participant, parent, or guardian may have, and an assessment of understanding, before proceeding to informed consent and assent decisions. Informed consent and assent processes will be fully documented, consistent with the DAIDS policies referenced in Section 12.2. Refer to Section 14.3 for further information on informed consent procedures for this study.

Each site must establish SOPs for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrollment. Sites are encouraged to minimize the time from screening to enrollment.

Eligibility screening will be initiated after written informed consent and assent (as applicable) is provided. See Section 4.7.2 below for use of the Subject Enrollment System to assist in tracking of the screening process and obtaining a study-specific screening number. Screening will include confirmatory HIV-1 testing (if needed) and assessment of other entry criteria. If at any time it is determined that an individual is not eligible for the study, or that study participation may not be feasible or in the participant’s best interest, the eligibility screening process will be discontinued; these individuals should be actively referred to non-study sources of care. Screening assessments, unless otherwise noted (see Section 6.2), must be completed within 28 days prior to entry; re-screening is permitted one time per Cohort. For adolescents who are screened and found to be ineligible for the study, or who do not enroll in the study for any reason, limited demographic information and reasons for non-enrollment will be entered into electronic case report forms (eCRFs). Refer to Section 9.5 for more information on monitoring participant accrual in this study.

4.7.2 Enrollment Process for Cohort 1 (Step 1) and Cohort 2 (Step 3) Participants

Adolescents who are found to meet the study eligibility criteria will be enrolled into the applicable Cohort and Step. Screening procedures may be performed on the day of enrollment; however, all required screening laboratory test results must be available for eligibility determination prior to enrollment.

The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent and assent (as applicable) are obtained for the adolescent, participant identification numbers (PIDs) will be assigned and a study-specific screening number will be obtained through the SES. For adolescents found to be eligible, enrollment into the study or into a subsequent step will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID) and the prescribing information for the Cohort and Step in which the participant has been enrolled.

4.8 Participant Retention

Once a participant is enrolled in this study, study staff will make every effort to retain him or her for the protocol-specified duration of follow-up, thereby maximizing statistical power and
minimizing potential biases associated with loss to follow-up. Each site must establish and implement SOPs that target retention rates that are sufficient to allow the primary study outcomes to be reliably estimated (a maximum 10% loss to follow-up is assumed in sample size calculations). Additional guidance regarding special considerations for retaining adolescents and particularly Cohort 2 participants no longer on pre-study cART regimen, are provided in the IMPAACT 2017 MOP. Refer to Section 9.5 for more information on monitoring participant retention in this study.

5 STUDY PRODUCT

Site pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. Refer to Figure 1, Figure 2, Figure 3, and Figure 4 for an overview of the cohorts, and study design, and to the package inserts and investigator’s brochures (IBs) for further information about the study products.

5.1 Study Product Regimen and Administration

Study participants will be assigned to receive (open-label) either CAB (oral CAB followed by intramuscular CAB LA) or RPV (oral RPV followed by intramuscular RPV LA) in Cohort 1. Study arm assignments in Cohort 1 will be based on participants’ pre-study cART regimen (as described in Section 5.1.1 below).

In Cohort 2, study participants will be assigned to receive (open-label) both CAB and RPV (oral CAB + oral RPV, followed by intramuscular CAB LA + intramuscular RPV LA).

5.1.1 Cohort 1

Participants in Cohort 1 will be assigned to Cohort 1C (oral CAB followed by intramuscular CAB LA) or Cohort 1R (oral RPV followed by intramuscular RPV LA) based on their pre-study cART regimen:

- Participants on a PI-based and/or NNRTI-based cART regimen will be assigned to Cohort 1C
- Participants on a INSTI-based cART regimen will be assigned to Cohort 1R

All participants in Cohort 1 will continue their pre-study cART regimen and receive either CAB (Cohort 1C) or RPV (Cohort 1R) as shown in Table 5.
### Table 5. Cohort 1: Study Product Regimen and Administration

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Step</th>
<th>Study Product Regimen and Administration (with non-study provided cART regimen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1C</td>
<td>1</td>
<td>CAB administered orally as one 30 mg tablet once daily, beginning at the Entry visit, for 4-6 weeks, with or without food.</td>
</tr>
<tr>
<td>1C</td>
<td>2</td>
<td>CAB LA administered as one IM injection in the gluteus medius at Week 4b (Step 2 Entry) study visit (600 mg/3 mL), at Week 8 (400 mg/2 mL), and at Week 12 (400 mg/2 mL).</td>
</tr>
<tr>
<td>1R</td>
<td>1</td>
<td>RPV administered orally as one 25 mg tablet once daily, beginning at the Entry visit, for 4-6 weeks, with a meal.</td>
</tr>
<tr>
<td>1R</td>
<td>2</td>
<td>RPV LA administered as one IM injection in the gluteus medius at Week 4b (Step 2 Entry) study visit (900 mg/3 mL), at Week 8 (600 mg/2 mL), and at Week 12 (600 mg/2 mL).</td>
</tr>
</tbody>
</table>

Study participants will receive the first dose of intramuscular CAB LA (Cohort 1C) or intramuscular RPV LA (Cohort 1R) on the same day as the last dose of oral CAB dose or oral RPV, respectively (at the Week 4b Step 2 Entry visit).

#### 5.1.2 Cohort 2

All participants in Cohort 2 will discontinue their pre-study cART regimen and receive both CAB and RPV as shown in Table 6. Cohort 2 doses may change based on experience in Cohort 1, in which case, the new doses will be specified in a letter of amendment or full amendment.

### Table 6. Cohort 2: Study Product Regimen and Administration

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Step</th>
<th>Study Product Regimen and Administration (without cART regimen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3</td>
<td>CAB administered orally as one 30 mg tablet once daily AND RPV administered orally as one 25 mg tablet once daily, taken together and with a meal, beginning at the Entry visit for 4-6 weeks.</td>
</tr>
</tbody>
</table>
| 2      | 4    | **First injection:** CAB LA administered as one 600 mg (3 mL) IM injection in the gluteus medius AND RPV LA administered as one 900 mg (3 mL) IM injection in the gluteus medius, at Week 4b (Step 4 Entry).  
**Subsequent injections:** CAB LA administered as a 400 mg (2 mL) IM injection in the gluteus medius muscle AND RPV LA administered as a 600 mg (2 mL) IM injection in the gluteus medius, every four weeks through Week 96. |

Study participants will receive the first doses of intramuscular CAB LA and intramuscular RPV LA on the same day as the last doses of oral CAB and oral RPV (at the Week 4b Step 4 Entry visit).
5.1.3 Dispensing of Oral Study Product (Cohort 1 Step 1, or Cohort 2 Step 3)

A 30-day supply of oral study product will be provided at the Entry visit (Cohort 1 and Cohort 2). Cohort 1 participants will be provided a 30-day supply of only the oral study product to which they are assigned, whereas Cohort 2 participants will be provided a 30-day supply of each oral study product.

An additional 30-day supply of oral study product may be dispensed at the Week 2 or Week 4a visits (Cohort 1 and Cohort 2) to ensure sufficient coverage for daily use through the participant’s scheduled Week 4b visit and their first study product injection. See Sections 6.3.4 and 6.4.4 for more details on the Cohort 1 Step 1 Week 4b visit, and Cohort 2 Step 3 Week 4b visit, respectively.

In exceptional circumstances, to address pre-planned missed CAB LA + RPV LA injection visits, following consultation with the CMC, sites may provide daily oral CAB 30 mg + RPV 25 mg as a short-term bridging strategy for Cohort 2 Step 4 participants who will miss a subsequent scheduled injection visit. Cohort 2 Step 4 participants may be required to repeat the loading doses of CAB LA + RPV LA (i.e. the Week 4b study product injection doses) should the participant be on oral bridging for more than 4 weeks, and/or have missed the Week 8 or Week 12 visits, and/or have missed three consecutive study product injections. The CMC must be consulted for treatment and dosing requirements prior to resuming study product injections.

See Section 6.1 for further guidance on scheduling study visits.

5.1.4 Preparation and Administration of Injections

The Pharmacist of Record must be proficient in the preparation of products requiring aseptic technique under a pharmacy biological safety cabinet/isolator. Local regulations and site institutional policies and procedures for use of protective equipment, such as gloves, gowns, and masks, and safety glasses, must be followed.

All injections will be administered using standard IM injection technique in the gluteus medius. The following information must be source documented and entered into eCRFs with each injection of study product (e.g. Cohort 2 Step 4 participants will have information entered for CAB LA, and information entered for RPV LA):

- Location (which side) of administration
- Needle length and needle gauge used
- Volume of injectable study product administered

Whenever possible, for Cohort 2 Step 4 participants, CAB LA is to be administered in the contralateral gluteus medius muscle from the RPV LA. However, if the participant prefers, injections can both be administered on the same side with the injection sites at least 2cm apart. In these instances, site staff must source document where on the gluteus medius muscle each injection has been administered for assessing adverse reactions to the injections.

Injectable study product must be administered within the respective study visit windows; see Section 6.1 for visit window requirements.

Refer to the IMPAACT 2017 MOP for detailed instructions on the preparation and administration of the study products.
5.2 **Study Product Formulation**

5.2.1 **Oral CAB**

CAB 30 mg tablets are formulated as white to almost white oval-shaped film-coated tablets for oral administration. The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closures that include an induction seal. The bottles contain 30 tablets and a desiccant. The tablets should be stored up to 30°C (86°F), in the original container with the desiccant, and protected from moisture.

5.2.2 **Oral RPV**

RPV 25 mg tablets are formulated as white to off-white, film-coated, round, biconvex tablets for oral administration. Tablets are packaged in bottles containing 30 tablets. Tablets should be stored in their original bottles to protect from light. The tablets should be stored at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F). Further information on the study product is available in the EDURANT® Prescribing Information.

5.2.3 **Injectable CAB LA**

CAB LA is formulated as a sterile white to slightly pink suspension containing 200mg/mL of cabotegravir free acid for administration by IM injection. The product is packaged in a 3-mL glass vial. Each vial is for single use and contains a nominal fill volume of 2 mL (400 mg of CAB LA). Dilution is not required prior to administration. Vials should be stored up to 30°C (86°F); do not freeze.

5.2.4 **Injectable RPV LA**

RPV LA is formulated as a sterile white suspension containing 300 mg/mL of RPV free base for administration by IM injection. The product is packaged in 4-mL vials. Each vial is for single use and contains a nominal fill volume of 2 mL (600 mg of RPV LA). Dilution is not required prior to administration. Vials should be stored refrigerated at 2° to 8°C (36° to 46°F); protect from light and do not freeze.

5.2.5 **Study Product Regulatory Approval Status**

The following study products being tested in this study are investigational and not yet approved by the US FDA for the treatment or prevention of HIV-1 infection: oral cabotegravir, injectable cabotegravir long-acting, injectable rilpivirine long-acting. Further information on the study product is available in the Investigator’s Brochure, which will be provided by the DAIDS Regulatory Support Center (RSC).

The oral rilpivirine study product being used in this study is approved by the US FDA for the treatment of HIV-1 infection in patients ages 12 years and older. Further information on the study product is available in the EDURANT® Prescribing Information.

5.3 **Study Product Supply**

CAB and CAB LA (oral and injectable formulations), and RPV and RPV LA (oral and injectable formulations) will be supplied by ViiV Healthcare.
The above-listed study products will be made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). Upon successful completion of protocol registration procedures, these study products may be obtained by the site pharmacist by following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

### 5.4 Study Product Accountability

Site pharmacists must maintain complete records of all study products received from the CRPMC and subsequently dispensed to study participants. All study products must be stored in the pharmacy.

### 5.5 Final Disposition of Study Product

Participants who temporarily or permanently discontinue oral study product during Step 1 or Step 3, or during oral bridging in Step 4, will be instructed to return all oral study products to the site clinic as soon as possible.

All unused study products remaining at US sites after the study is completed or terminated will be returned to the CRPMC (unless otherwise directed by DAIDS). Study products may also be returned to the CRPMC for other reasons, as requested by DAIDS. Site pharmacists will follow the relevant instructions for return or destruction of unused study products provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

### 5.6 Concomitant Medications

All concomitant medications received by enrolled participants must be source documented as part of the medical and medication histories obtained at each study visit. This includes prescription and non-prescription (over-the-counter) medications; vaccines and other preventive medications; therapeutic foods and nutritional supplements; and alternative, complementary, and traditional medications and preparations. All concomitant medications (except herbal or traditional) are to be entered into eCRFs, per Section 6.10.

CART, other than CAB and RPV (oral and injectable formulations), will not be provided through the study.

### 5.7 Prohibited Medications

Any study participant who requires a medication considered prohibited while on study product must have the study product held or permanently discontinued. A list of prohibited medications may be found on the IMPAACT 2017 protocol-specific website (http://impaactnetwork.org/studies/IMPAACT2017.asp). Upon identification of the need for a prohibited medication, the site investigator should consult the CMC for further guidance on study product management, and per Section 8.

### 5.8 Precautionary Medications

A list of medications that should be used with caution while on study product may be found on the IMPAACT 2017 protocol-specific website.
6 STUDY VISITS AND PROCEDURES

All visits and procedures must be performed at the approved clinical research site or approved associated facilities (with the exception of the qualitative phone interview; see Section 11). All visits and procedures must be documented in accordance with the NIAID Division of AIDS (DAIDS) policies for source documentation; refer to Section 12 for more information on data handling and record keeping. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent and/or assent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be conducted and documented consistent with site SOPs. Study staff should inform participants (or parents/guardians, if applicable) of clinically meaningful physical exam findings and laboratory test results, when available. See Section 14.9 for additional considerations of disclosing test results to the parents/guardians of adolescent participants.

Information relating to study visit windows, and split and interim visits is described in Section 6.1, including additional considerations for scheduling injection visits. Detailed information related to specific visits, such as target visit dates, individual visit windows, required procedures per scheduled visits, and further guidance for select procedures are presented in Sections 6.2-6.16. See Section 5.1.4 for source documentation and eCRF requirements for any study product injection. Procedures required to continue oral and injectable study product administration at scheduled follow-up visits are described in Section 6.9.

PK sample collections are required at visits throughout Cohort 1, Cohort 2, and LS FU. All pre-dose PK sample collections should be performed prior to and on the same day as administration of the specified study product. The date and time of each PK sample collection must be source documented and entered into eCRFs for all PK samples. Additional source documentation, eCRF requirements, and scheduling considerations for PK sample collections during Weeks 2, and 4b (for both Cohorts 1 and 2) are provided in the relevant visit sections below.

Site staff collecting specimens for PK evaluations must prepare workspace and supplies with regards to protecting all PK specimens from light, as specified in the LPC. As Cohort 2 participants will receive both CAB and RPV, the PK sample collection must be sufficient for the number of aliquots specified in the LPC for CAB and for RPV. Albumin (g/dL) will be obtained as part of blood collection for chemistries, but only at visits in which both chemistries and a PK sample are collected. See Section 6.16 for details on specimen collection considerations and processing, and Appendix I-A, Appendix I-B, and Appendix I-C for required blood volumes.

6.1 Study Visit Windows, Split and Interim Visits

6.1.1 Study Visit Windows and Additional Considerations for Injection Visits

For follow-up study visits, a target visit date and a target visit window are specified. Study visits should be scheduled to occur on the respective target visit date. If it is not possible to conduct a visit on the respective target visit date, the visit may be scheduled within the target visit window. Additionally, for specified Cohort 1 and Cohort 2 visits (i.e. all injection visits, the Week 2 visit,
and the Cohort 1 Week 9 visit), broader allowable visit windows are also provided. If the participant is unable to attend the scheduled study visit on the target visit date or within the target window, study visits may be conducted within the allowable windows.

In brief, study product injection visit target dates are based on the participant’s first study product injection administered for the applicable Step (the Step 2 Week 4b visit, or the Step 4 Week 4b visit). Target visit windows and broader allowable visit windows are provided for study product injection visits. In addition to the specified visit windows, study product injections should be scheduled a minimum of 3 weeks (21 days) and a maximum of 5 weeks (35 days) apart, as counted from the previous injection.

When scheduling and conducting study visits in which injectable study product is administered, the CMC must be notified of the following:

- Administering study product injections outside of the 3 to 5-week spacing timeframe
- Administering study product injections within the allowable window (and outside of the target date and target window)

CMC notification should ideally occur prior to administering study product injections in the above scenarios, although a CMC response is not required prior to administration of injectable study product. However, after administration of injectable study product in the above scenarios and prior to the participant’s next scheduled injection visit, sites must consult the CMC regarding additional clinical considerations and injection visit scheduling.

For missed study product injections (i.e. the scheduled study product injection does not occur within either the target or allowable windows of the respective visit), the CMC must be consulted and guidance on clinical considerations and study product management received prior to administration of the next scheduled study product injection.

Sites are expected to make every effort to schedule and conduct each study visit on the respective target visit date, or, when necessary, within the target visit window. Further guidance on scheduling study visits are provided in the IMPAACT 2017 Manual of Procedures (MOP).

### 6.1.2 Split and Interim Visits

All visit procedures specified to be performed at scheduled visits should ideally be performed on the same day. However, if it is not possible to conduct all visit procedures on the same day (e.g., if a participant must leave the clinical research site before all procedures can be performed), visits may be split, with procedures performed on more than one day. See Section 6.9 for required study visit procedures to be performed on the same day as and prior to administration of study product.

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the site investigator or designee at any time during the study, and without prior approval from the CMC. Some interim visits may occur for administrative reasons or retention purposes. Interim visits at which no data are collected should be source documented but not entered into eCRFs. Other interim contacts and visits may occur in response to adverse events (AE) experienced by study participants. When interim contacts or visits are completed in response to participant reports of adverse events, study staff will assess the reported event clinically, enter the event into eCRFs per Section 7.2, and provide or refer the participant to appropriate medical care. See Section 8 for participant management and specified AE management.
Further details and guidance on scheduling and conducting visits are provided in the IMPAACT 2017 MOP.

### 6.2 Cohort 1 Step 1, and Cohort 2 Step 3 Screening Visit

Refer to Section 4.7 for a description of the study recruitment, screening, and enrollment process.

Screening may be initiated after written informed consent/assent is obtained. All screening procedures must be performed within 28 days prior to study entry. Hematology, chemistries, HIV-1 RNA, pregnancy testing, and confirmation of HIV infection (if necessary) are required, in relation to the eligibility criterion in Sections 4.1-4.2; as soon as the required laboratory screening test results are obtained, all results should be graded for severity as specified in Section 7.3.3. Multiple visits may be conducted within the 28-day time frame to complete all required procedures and to repeat laboratory tests for confirmation, if necessary.

<table>
<thead>
<tr>
<th>Cohort 1 Step 1, and Cohort 2 Step 3, Screening Visit Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative and Regulatory</strong></td>
</tr>
<tr>
<td>• Obtain written informed consent/assent</td>
</tr>
<tr>
<td>• Assign PID to adolescent</td>
</tr>
<tr>
<td>• Obtain screening number from SES</td>
</tr>
<tr>
<td>• Obtain available documentation of participant’s HIV status</td>
</tr>
<tr>
<td>• Collect demographic and locator information</td>
</tr>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
</tr>
<tr>
<td>• Provide HIV pre-/post-test counseling, if indicated</td>
</tr>
<tr>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain available medical records and medical and medications history</td>
</tr>
<tr>
<td>• Assess documentation of HIV infection</td>
</tr>
<tr>
<td>• Assess ARV history</td>
</tr>
<tr>
<td>• Assess HIV-1 RNA test result history</td>
</tr>
<tr>
<td>• Perform complete physical exam</td>
</tr>
<tr>
<td>• Perform Sexual Maturity Rating</td>
</tr>
<tr>
<td>• Perform an ECG (in triplicate)</td>
</tr>
<tr>
<td>• For Cohort 1 participants screening for Cohort 2, confirm completion of all Cohort 1 Step 2 study visits</td>
</tr>
<tr>
<td><strong>Laboratory Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Confirmatory HIV testing, if needed per Section 4.1.6</td>
</tr>
<tr>
<td>• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)</td>
</tr>
<tr>
<td>• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl: Schwartz formula ml/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN)</td>
</tr>
<tr>
<td>• HIV-1 RNA</td>
</tr>
<tr>
<td>• Store plasma for genotypic and phenotypic resistance testing</td>
</tr>
<tr>
<td><strong>Blood or Urine</strong></td>
</tr>
<tr>
<td>• For females, collect blood or urine for pregnancy test</td>
</tr>
</tbody>
</table>

For potential participants who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined and these individuals should be actively referred to non-study sources of care. See Section 4.7.1 for documentation requirements for adolescents who are found to be ineligible.
Participants may rescreen once per Cohort (i.e. total of two screening attempts for Cohort 1 and two screening attempts for Cohort 2 are allowed). If any participant is re-screened, all screening procedures listed above must be repeated, with the exception that:

- A new PID should not be assigned (Note: Obtain new screening number from SES for second screening attempt)
- Confirmatory HIV testing, if conducted during first screening attempt, need not be repeated
- Previously documented medical and medications history information should be reviewed and updated through the date of re-screening (it is not necessary to re-record history information that was previously documented)

The Cohort 1 Entry Visit (Step 1 – oral phase) is described in Section 6.3.1. The Cohort 2 Entry Visit (Step 3 – oral phase) is described in Section 6.4.1.

Additional Considerations for Cohort 1 Step 2 Participants Screening for Cohort 2 Step 3

Cohort 2, Step 3 will initially open to accrual limited to adolescents who have completed the Cohort 1 Step 2 Week 16 study visit. These participants must undergo screening procedures to determine Cohort 2, Step 3 eligibility, should they wish to participate in Cohort 2. The timing of screening and, if eligible, enrolling into Cohort 2 Step 3 may occur prior to completing all scheduled LSFU study visits. In the event Cohort 1 Step 2 participants complete all scheduled LSFU study visits and exit the study (as described in Section 6.5 below), these former Cohort 1 Step 2 participants may undergo screening procedures to determine eligibility for resuming study participation in Cohort 2 Step 3.

Any adolescent screening for Cohort 2, Step 3 is required to meet eligibility criteria per Sections 4.1-4.2, regardless of previous Cohort 1 study participation. Clinical assessments, evaluations, and laboratory values obtained during Cohort 1 Step 2 or LSFU study visits may be used to screen for Cohort 2 eligibility, if obtained within 28 days of the Cohort 2 Entry Visit. Otherwise, all screening visit procedures as described above must be completed for Cohort 2 Step 3 eligibility determination. For previous Cohort 1 Step 2 participants, a new screening number will not be obtained from SES for the Cohort 2 Step 3 screening attempt.

Any adolescent found to meet the applicable eligibility criteria will be enrolled into Cohort 2 Step 3, per Section 4.7 and Section 6.4.1. Previous Cohort 1 Step 2 participants will retain their PID as assigned during Cohort 1 procedures and a new SID will be assigned upon successful enrollment using the SES.

Additional guidance and eCRF completion processes for (former) Cohort 1 Step 2 participants enrolling into Cohort 2 Step 3 may be found in the IMPAACT 2017 MOP.

6.3 Cohort 1

6.3.1 Cohort 1 Entry Visit (Step 1 – oral phase)

Refer to Section 4.7 for a description of the study recruitment, screening, and enrollment processes. The Cohort 1 Step 1 Entry visit must occur within 28 days (inclusive) from the Cohort 1 Screening Visit. Cohort 1 Step 1 Entry visit procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination and
enrollment. In the event a participant is found to be ineligible on the day of enrollment, enrollment should not occur.

The following visit procedures must be conducted during the Cohort 1 Step 1 Entry Visit in the sequence specified below:

- Complete final eligibility determination and confirmation (medical and medications history including ARV history assessment, symptom-directed physical exam, an ECG if indicated, and, for females, pregnancy testing); for females, pregnancy test results must be available for eligibility confirmation
- Complete a paper-based Step 1 eligibility checklist
- Enroll the participant on Cohort 1 Step 1 and obtain SID
- Prescribe assigned oral study product
- Dispense assigned oral study product
- Facilitate and observe administration of assigned oral study product

Note that acceptability and tolerability questionnaires must be administered relative to other Entry visit procedures as specified in the IMPAACT 2017 MOP. Visit procedures not otherwise specified may be conducted at any timepoint during the Cohort 1 Step 1 Entry visit. Operational guidance on the order of Entry visit procedures may be found in the IMPAACT 2017 MOP.

<table>
<thead>
<tr>
<th>Cohort 1 Step 1 Entry Visit Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative and Regulatory</td>
</tr>
<tr>
<td>• Complete final eligibility determination and confirmation*</td>
</tr>
<tr>
<td>• Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file</td>
</tr>
<tr>
<td>Behavioral and Counseling</td>
</tr>
<tr>
<td>• Provide adherence counseling</td>
</tr>
<tr>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td>• Perform acceptability/tolerability assessment questionnaires</td>
</tr>
<tr>
<td>Clinical</td>
</tr>
<tr>
<td>• Update medical and medications history since last visit*</td>
</tr>
<tr>
<td>• Perform symptom-directed physical exam*</td>
</tr>
<tr>
<td>• Assess ARV history*</td>
</tr>
<tr>
<td>• Perform an ECG, if indicated*</td>
</tr>
<tr>
<td>Laboratory</td>
</tr>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)</td>
</tr>
<tr>
<td>• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl: Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN)</td>
</tr>
<tr>
<td>• CD4 count and percentage</td>
</tr>
<tr>
<td>• HIV-1 RNA</td>
</tr>
<tr>
<td>• Store plasma for genotypic and phenotypic resistance testing</td>
</tr>
<tr>
<td>Blood or Urine</td>
</tr>
<tr>
<td>• For females, collect blood or urine for pregnancy test*</td>
</tr>
<tr>
<td>Study Product</td>
</tr>
<tr>
<td>• Prescribe, dispense, and facilitate administration of the assigned oral study product, see Section 5.1</td>
</tr>
</tbody>
</table>

*Perform prior to enrollment
6.3.2 Cohort 1 Week 2 Visit (Step 1 – oral phase)

The Cohort 1 Week 2 visit is targeted to be conducted on day 14, counted from the day of entry, with a target window of +7 days from the target date. If necessary, this visit may be conducted within the allowable window of +14 days from the target date and the CMC notified.

PK samples will be collected at the Week 2 visit and over a 24-hour period; Cohort 1C and Cohort 1R will have different PK sample collection timepoints at the Week 2 visit only. The pre-dose PK sample collection should be performed prior to and on the same day as the oral study product dose observed at the site. See the procedural table below for the specific PK collection time points and collection windows.

After the Entry visit and through the Week 2 visit, participants should be recommended to take the oral study product at the same time of day (morning or evening) as the Week 2 visit pre-dose PK collection time point. At minimum, for the three days prior to the Week 2 visit, participants should take their oral study product at the same time of day (morning or evening) as the scheduled pre-dose PK collection time point, and be fully adherent to their assigned daily oral study product regimen. In preparation for the Week 2 visit, sites may contact participants or parents and guardians, to reinforce adherence within the three days prior to the scheduled PK evaluation using retention methods as described in Section 4.8, as well as to remind the participant to hold the oral study product dose due on the day of the Week 2 visit. For example, sites may call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence.

If, for the three days prior to the Week 2 visit, either a missed dose is reported or the participant has not adjusted the timing of their oral study product dosing to align with the pre-dose PK collection time point, the Week 2 visit should be rescheduled. Additional guidelines for scheduling and conducting the Cohort 1 Week 2 visit are below.

- Participants and their parents/guardians should be reminded to hold administration of the daily oral study product due on the day of the Week 2 visit, to allow for a pre-dose PK sample collection and for the dose to be observed at the site. The Week 2 visit should be rescheduled if the oral study product dose was already taken and not observed at the site.
- Participants and their parents/guardians should also be reminded to return all oral study product at the Week 2 visit, such that the adherence assessment may be performed.
- Height and weight must be obtained on the same day as initiating the Week 2 PK evaluation.
- Cohort 1R participants should be provided food or a meal with the observed oral study product dose; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements
- The oral study product dose dates, times, dose amounts, and food intake around the oral doses must be source documented and entered into eCRFs for the oral doses observed at the Week 2 visit in addition to the previous three doses.
- For participants who report intercurrent illness immediately prior to or on the day of the scheduled PK visit that may have interfered with study product administration or resulted in malabsorption of study product (e.g., fever, vomiting, diarrhea), the Week 2 visit should be rescheduled.
- If the observed oral study product dose is not retained within 30 minutes (inclusive) of administration (e.g., vomiting), the Week 2 visit should be rescheduled.
- Depending on site capacity and participant preferences, participants and their parents or guardians may stay at the clinical research facility overnight for the PK sampling.
Additional oral study product, as assigned per Cohort 1C or Cohort 1R, may be dispensed at this visit if needed to provide coverage until the Week 4a visit, per Section 5.1.3. Pregnancy test results must be obtained prior to any dispensing of additional oral study product.

Following the Week 2 visit, timing of taking the oral study product may be changed, if desired. However, participants should be encouraged to maintain the timing of taking their oral study product (morning or evening) through the Week 4b visit. Additional guidance regarding the timing of oral study product dosing prior to the Week 2 visit is provided in the IMPAACT 2017 MOP.

### Cohort 1 Week 2 Visit Procedures (Step 1 – oral phase)

| Behavioral and Counseling | • Provide adherence counseling  
|                          | • Provide contraceptive counseling  
|                          | • Perform acceptability/tolerability assessment questionnaires, *if indicated*  
| Clinical                | • Update medical and medications history since last visit  
|                          | • Perform symptom-directed physical exam (including height and weight)  
|                          | • Perform adherence assessment  
|                          | • Identify/review/update adverse events  
| Laboratory              | Blood Collect blood for:  
|                          | • Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)  
|                          | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
|                          | • HIV-1 RNA  
|                          | • Store plasma for genotypic and phenotypic resistance testing  
| Blood (PK evaluation)    | Collect blood for:  
|                          | • Cohort 1C: Pre-dose, 1, 2, 3, 4, 8, and 24 hours post-dose (7 PK collection timepoints)  
|                          | • Cohort 1R: Pre-dose, 4, 8, and 24 hours post dose (4 PK collection timepoints)  
|                          | ± 30 minutes window is allowed for the 4-hours post-dose; ± 1 hr window is allowed for the 8- and 24-hours post-dose; the 24-hours post-dose must be collected prior to the subsequent oral study product dose  
| Blood or Urine           | • For females, collect blood or urine for pregnancy test; result must be obtained before observed dose of oral study product  
| Study Product            | • Prescribe, dispense, and facilitate administration of the assigned oral study product, *if indicated, see Section 5.1*  

#### 6.3.3 Cohort 1 Week 4a Visit (Step 1 – oral phase)

The Cohort 1 Week 4a visit is targeted to be conducted on day 28, counted from the day of entry, with a target window of +7 days from the target date, and an allowable window of -7 days/+10 days from the target date.

Participants and their parents/guardians should be reminded to return all oral study product at the Week 4a visit, such that the adherence assessment may be performed. Additional oral study product, as assigned per Cohort 1C or Cohort 1R, may be dispensed at this visit if needed to provide coverage until the Week 4b visit, per Section 5.1.3. Pregnancy test results must be obtained prior to any dispensing of additional oral study product.
Data collected through the Week 4a study visit will be assessed to determine eligibility to enter Step 2 and receive injectable CAB LA or RPV LA, per Cohort 1C or Cohort 1R, respectively. Week 4a visit laboratory test results should be reviewed as soon as they are available, for determining Step 2 eligibility and scheduling the Week 4b visit. Abnormal laboratory test result values from the Week 4a visit may be repeated prior to scheduling the Week 4b visit. If repeat laboratory test results confirm Step 2 eligibility, and all other eligibility criteria are met, the Week 4b visit may be scheduled within the target visit window (see Section 6.3.4 below) for Step 2 Entry and injectable study product administration, and may be combined with the Week 4a visit. See Section 4.3 for Cohort 1 Step 2 eligibility criteria.

If Cohort 1 participants are ineligible to receive injectable study product in Step 2, they will permanently discontinue oral study product use and complete an Early Termination visit 28 days after their last oral study product dose (see Section 6.5.5).

### Cohort 1 Week 4a Visit Procedures (Step 1 – oral phase)

<table>
<thead>
<tr>
<th>Behavioral and Counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provide adherence counseling</td>
</tr>
<tr>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td>• Perform acceptability/tolerability assessment questionnaires, if indicated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Update medical and medications history since last visit</td>
</tr>
<tr>
<td>• Perform complete physical exam</td>
</tr>
<tr>
<td>• Perform adherence assessment</td>
</tr>
<tr>
<td>• Identify/review/update adverse events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)</td>
</tr>
<tr>
<td>• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood or Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For females, collect blood or urine for pregnancy test; result must be obtained before dispensing oral study product, if dispensing is indicated at this visit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study product</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prescribe, dispense, and facilitate administration of the assigned oral study product, if indicated, see Section 5.1</td>
</tr>
</tbody>
</table>

6.3.4 Cohort 1 Week 4b Visit (Step 2 Entry – injection phase)

The Week 4b visit must take place after Week 4a laboratory test results are available, and with the target visit window of day 21-42, counted from the day of Step 1 entry. This visit should be scheduled to minimize the time between the Week 4a visit and initiation of the injectable study products in Step 2. Additionally, the Week 4b visit must occur within 42 days (inclusive) of Step 1 entry so as not to exceed the intended maximum of 6 weeks on oral study product.

Cohort 1 participants who meet eligibility criteria per Section 4.3 to progress to Step 2 will receive their last oral dose of CAB or RPV on the same day as their first injection of CAB LA or RPV LA at the Week 4b study visit, which also serves as the Step 2 Entry visit. Note that HIV-1 RNA test results collected at the Week 4b visit are not required to be obtained or reviewed prior to administering injectable study product.

PK samples will be collected at the Week 4b visit. After the Week 2 visit and through the Week 4b visit, participants should be recommended to take the oral study product at the same time of day (morning or evening) as the Week 4b visit pre-dose PK collection time point. For the three days prior to the Week 4b visit, participants should ideally take their oral study product at the
same time of day (morning or evening) as the scheduled pre-dose PK collection time point, and be fully adherent to their assigned daily oral study product regimen. However, the Week 4b visit may continue as scheduled if a missed dose is reported, or the participant has not adjusted the timing of their oral study product dosing to align with the pre-dose PK collection time point.

In preparation for the Week 4b visit, sites may contact participants or parents and guardians, to reinforce adherence and oral study product dose timing within the three days prior to the scheduled PK evaluation using retention methods as described in Section 4.8. For example, sites may call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence. Participants and their parents/guardians should be reminded to hold administration of the daily oral study product due on the day of the Week 4b visit, to allow for a pre-dose PK sample collection and for the dose to be observed at the site. Participants and their parents/guardians should also be reminded to return all oral study product at the Week 4b visit, such that the adherence assessment may be performed.

Prior to initiating the pre-dose PK sample collection, study staff should ascertain when the participant’s most recent oral study product dose was administered to determine whether oral study product should be administered during Week 4b visit:

- If the participant’s most recent oral study product dose was taken more than 12 hours from the Week 4b pre-dose PK sample collection, the pre-dose PK sample should be collected prior to observing the participant’s last oral study product dose administered (and observed) at the site. Sites should provide Cohort 1R participants food or a meal with the observed oral study product dose; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements.

- If the participant’s most recent oral study product dose was taken within 12 hours (inclusive) of the Week 4b pre-dose PK sample collection, an oral study product dose may not be administered during Week 4b visit. The Week 4b visit may still occur as scheduled and the pre-dose PK sample collection will be prior to the participant’s first study product injection.

The following Cohort 1 Week 4b visit procedures must be conducted on the same day (may not be conducted over a multi-day split visit) and as specified below:

- Contraceptive and adherence counseling must be provided prior to enrolling the participant into Step 2 to confirm the participant is willing to receive the injectable study product.
- Final eligibility determination and confirmation must be completed prior to completing the Step 2 eligibility checklist: medical and medications history, symptom-directed physical exam (must include height and weight), adherence assessment, and, for females, pregnancy testing; for females, pregnancy test results must be available for eligibility confirmation.
- The pre-dose PK sample must be collected prior to the participant’s first study product injection. See guidance above regarding whether the pre-dose PK sample is collected prior to an oral study product dose administered (and observed) at the site, or whether no oral study product dose is administered at this visit.
- The Step 2 paper-based eligibility checklist must be completed prior to enrolling the participant to Step 2.
- Enrollment to Step 2 must occur prior to prescribing the assigned injectable study product.
- Prescribing must occur prior to dispense assigned injectable study product.
- Administration of the assigned injectable study product must occur after enrollment into Step 2, and after prescribing and dispensing the participant’s assigned injectable study product.
- The post-dose PK sample must be collected after administration of both the oral study product and the injectable study product.
Note that acceptability and tolerability questionnaires must be administered relative to other Week 4b visit procedures as specified in the IMPAACT 2017 MOP. Visit procedures not otherwise specified may be conducted at any timepoint during the Week 4b visit. Operational guidance on the order of Week 4b visit procedures may be found in the IMPAACT 2017 MOP.

### Cohort 1 Week 4b Visit Procedures (Step 2 Entry - injection phase)

| Behavioral and Counseling | • Provide contraceptive counseling*  
|                          | • Provide adherence counseling*  
|                          | • Perform acceptability/tolerability assessment questionnaires  
|                          | • Conduct qualitative phone interview, if indicated, see Section 11 |
| Administrative and Regulatory | • Complete final eligibility confirmation for Step 2 Entry, see Section 4.3*  
|                          | • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file  
| Clinical | • Update medical and medications history since last visit*  
|          | • Perform symptom-directed physical exam*  
|          | • Identify/review/update adverse events*  
|          | • Perform adherence assessment*  
| Laboratory | Collect blood for:  
| Blood | • HIV-1 RNA  
|          | • Store plasma for genotypic and phenotypic resistance testing  
|          | • PK evaluation: Pre-dose and 2 hours post-dose (2 PK collection timepoints), ± 30 minutes window is allowed for the 2-hours post-dose  
| Blood or Urine | • For females, collect blood or urine for pregnancy test*  
| Study product | • Prescribe, prepare, and administer assigned injectable study product, see Section 5.1  

*Perform prior to completing the Step 2 eligibility checklist and prior to prescribing injectable study product.

#### 6.3.5 Cohort 1 Week 5 Visit (Step 2 – injection phase)

The Week 5 visit is targeted to be conducted 3 days after completion of the Week 4b Step 2 Entry visit (the first administration of injectable study product), with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

### Cohort 1 Week 5 Visit Procedures (Step 2 - injection phase)

| Behavioral and Counseling | • Provide contraceptive counseling  
|                          | • Perform acceptability/tolerability assessment questionnaires, if indicated  
|                          | • Conduct qualitative phone interview, if indicated, see Section 11 |
| Clinical | • Update medical and medications history since last visit  
|          | • Perform symptom-directed physical exam  
|          | • Identify/review/update adverse events  
| Laboratory | Collect blood for:  
| Blood | • Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)  
|          | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl: Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
|          | • PK evaluation: Single sample  

6.3.6 **Cohort 1 Week 6 Visit (Step 2 – injection phase)**

The Week 6 visit is targeted to be conducted 10 days after completion of the Week 4b Step 2 Entry visit (the first administration of injectable study product), with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

<table>
<thead>
<tr>
<th>Cohort 1 Week 6 Visit Procedures (Step 2 - injection phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
</tr>
<tr>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td>• Perform acceptability/tolerability assessment questionnaires, <em>if indicated</em></td>
</tr>
<tr>
<td>• Conduct qualitative phone interview, <em>if indicated, see Section 11</em></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Update medical and medications history since last visit</td>
</tr>
<tr>
<td>• Perform symptom-directed physical exam</td>
</tr>
<tr>
<td>• Identify/review/update adverse events</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td><strong>Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• PK evaluation: Single sample</td>
</tr>
</tbody>
</table>

6.3.7 **Cohort 1 Week 8 Visit (Step 2 – injection phase)**

The Week 8 visit is targeted to be conducted 28 days after the Week 4b Step 2 Entry visit (the first administration of injectable study product), with a target window of -7 days/+3 days from the target date.

Sites are expected to make every effort to schedule and conduct the injection study visits on the target visit date, or, when necessary, within the target visit window. If the participant is unable to come to the study visit and all scheduling options within the target visit window are exhausted, this visit may be conducted within the allowable window of ± 14 days from the target date and the CMC notified.

<table>
<thead>
<tr>
<th>Cohort 1 Week 8 Visit Procedures (Step 2 - injection phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
</tr>
<tr>
<td>• Provide adherence counseling</td>
</tr>
<tr>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td>• Perform acceptability/tolerability assessment questionnaires</td>
</tr>
<tr>
<td>• Conduct qualitative phone interview, <em>if indicated, see Section 11</em></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Update medical and medications history since last visit</td>
</tr>
<tr>
<td>• Perform symptom-directed physical exam</td>
</tr>
<tr>
<td>• Identify/review/update adverse events</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td><strong>Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)</td>
</tr>
<tr>
<td>• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)</td>
</tr>
<tr>
<td>• HIV-1 RNA</td>
</tr>
<tr>
<td>• Store plasma for genotypic and phenotypic resistance testing</td>
</tr>
<tr>
<td>• PK evaluation: Single pre-dose sample</td>
</tr>
<tr>
<td><strong>Blood or Urine</strong></td>
</tr>
<tr>
<td>• For females, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product</td>
</tr>
<tr>
<td><strong>Study product</strong></td>
</tr>
<tr>
<td>• Prescribe, prepare, and administer assigned injectable study product, <em>see Section 5.1</em></td>
</tr>
</tbody>
</table>
6.3.8 Cohort 1 Week 9 Visit (Step 2 – injection phase)

The Week 9 visit is targeted to be conducted 3 days after completion of the Week 8 visit, with a target window of +7 days from the target date, to assess any signs or symptoms experienced since the Week 8 visit. The Week 9 visit may be conducted by telephone (voice or via text message), with study staff contacting participants or their parents/guardians, or with the participant attending the study clinic in person. Following any signs and symptoms reported via text message, study staff should follow-up with a voice telephone call or schedule an in-person visit for appropriate assessment. All contacts will be source documented. All reported signs and symptoms will be assessed for severity grading and entered into eCRFs as described in Section 7.2, and assessed for relationship to study product as described in Section 8.1.

Following a telephone contact, participants should be assessed in-person within the Week 9 target visit window to follow-up on any sign or symptom if severity grading cannot be determined over the phone, if any sign or symptom is determined to be Grade 3 or higher, or at the discretion of the investigator. If necessary, this visit may be conducted within the allowable window of -1 day/+10 days from the target date and the CMC notified.

| **Behavioral and Counseling** | • Provide contraceptive counseling  
| • Perform acceptability/tolerability assessment questionnaires (if indicated and in-person)  
| • Conduct qualitative phone interview, *if indicated, see Section 11* |
| **Clinical** | • Update medical and medications history since last visit (via telephone contact or in-person)  
| • Perform symptom-directed physical exam (if in-person)  
| • Identify/review/update adverse events (via telephone contact or in-person) |

6.3.9 Cohort 1 Week 12 Visit (Step 2 – injection phase)

The Week 12 visit is targeted to be conducted 56 days after the Week 4b Step 2 Entry visit (the first administration of injectable study product), with a target window of -7 days/+3 days from the target date.

Sites are expected to make every effort to schedule and conduct the injection study visits on the target visit date, or, when necessary, within the target visit window. If the participant is unable to come to the study visit and all scheduling options within the target visit window are exhausted, this visit may be conducted within the allowable window of ± 14 days from the target date and the CMC notified.
Cohort 1 Week 12 Visit Procedures (Step 2 - injection phase)

| Behavioral and Counseling | • Provide contraceptive counseling  
|                           | • Perform acceptability/tolerability assessment questionnaires  
|                           | • Conduct qualitative phone interview, *if indicated, see Section 11* |
| Clinical                  | • Update medical and medications history since last visit  
|                           | • Perform symptom-directed physical exam  
|                           | • Identify/review/update adverse events |

| Laboratory Blood          | Collect blood for:  
|                           | • Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)  
|                           | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
|                           | • HIV-1 RNA  
|                           | • Store plasma for genotypic and phenotypic resistance testing  
|                           | • PK evaluation: Pre-dose and 2 hours post-dose (2 PK collection timepoints), ± 30 minutes window is allowed for the 2-hours post-dose |

| Blood or Urine            | • For females, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product |

| Study product             | • Prescribe, prepare, and administer assigned injectable study product, *see Section 5.1* |

### 6.3.10 Cohort 1 Week 13 Visit (Step 2 – injection phase)

The Week 13 visit is targeted to be conducted 3 days after completion of the Week 12 visit (the third administration of injectable study product), with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

| Behavioral and Counseling | • Provide contraceptive counseling  
|                           | • Perform acceptability/tolerability assessment questionnaires, *if indicated* |
| Clinical                  | • Update medical and medications history since last visit  
|                           | • Perform symptom-directed physical exam  
|                           | • Identify/review/update adverse events  
|                           | • Perform an ECG |

| Laboratory Blood          | Collect blood for:  
|                           | • Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)  
|                           | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
|                           | • PK evaluation: Single sample |

### 6.3.11 Cohort 1 Week 14 Visit (Step 2 – injection phase)

The Week 14 visit is targeted to be conducted 10 days after completion of the Week 12 visit (the third administration of injectable study product), with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.
### Cohort 1 Week 14 Visit Procedures (Step 2 - injection phase)

| Behavioral and Counseling | • Provide contraceptive counseling  
|                          | • Performed acceptability/tolerability assessment questionnaires, if indicated  
| Clinical                 | • Update medical and medications history since last visit  
|                          | • Perform symptom-directed physical exam  
|                          | • Identify/review/update adverse events  
| Laboratory Blood         | Collect blood for:  
|                          | • PK evaluation: Single sample  

#### 6.3.12 Cohort 1 Week 16 Visit (Step 2 – injection phase)

The Week 16 visit is targeted to be conducted 28 days after completion of the Week 12 visit, with a target window of ±7 days from the target date, and an allowable window of ±14 days from the target date.

| Behavioral and Counseling | • Provide contraceptive counseling  
|                          | • Provide adherence counseling  
|                          | • Perform acceptability/tolerability assessment questionnaires  
| Clinical                 | • Update medical and medications history since last visit  
|                          | • Perform complete physical exam  
|                          | • Identify/review/update adverse events  
|                          | • Perform Sexual Maturity Rating  
|                          | • Perform an ECG  
| Laboratory Blood or Urine | Collect blood for:  
|                          | • Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)  
|                          | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
|                          | • CD4 count and percentage  
|                          | • HIV-1 RNA  
|                          | • Store plasma for genotypic and phenotypic resistance testing  
|                          | • PK evaluation: Single sample  
| Blood or Urine           | • For females, collect blood or urine for pregnancy test  

Participants completing the Cohort 1 Week 16 visit will be followed according to the LSFU visit schedule beginning with the LSFU Week 12 Visit (see Section 6.5 and Appendix I-C), or may screen for Cohort 2 eligibility if Cohort 2 has been opened to accrual.

### 6.4 Cohort 2

#### 6.4.1 Cohort 2 Step 3 Entry Visit

Refer to Section 4.7 for a description of the study recruitment, screening, and enrollment processes. The Cohort 2 Step 3 Entry visit must occur within 28 days (inclusive) from the Cohort 2 Screening Visit. Cohort 2 Step 3 Entry visit procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination and enrollment. In the event a participant is found to be ineligible on the day of enrollment, enrollment should not occur.
Specified visit procedures must be conducted during the Cohort 2 Step 3 Entry Visit in the sequence specified below:

- Complete final eligibility determination and confirmation (medical and medications history, symptom-directed physical exam, an ECG if indicated, and, for females, pregnancy testing); for females, pregnancy test results must be available for eligibility confirmation
- Complete a paper-based Step 3 eligibility checklist
- Enroll the participant on Cohort 2 Step 3 and obtain SID
- Prescribe oral study product
- Dispense oral study product
- Facilitate and observe administration of oral study product

Note that acceptability and tolerability questionnaires must be administered relative to other Entry visit procedures as specified in the IMPAACT 2017 MOP. Visit procedures not otherwise specified may be conducted at any timepoint during the Cohort 2 Step 3 Entry visit. Operational guidance on the order of Entry visit procedures may be found in the IMPAACT 2017 MOP.

Upon enrolling into Cohort 2, Step 3, study participants will discontinue their pre-study oral cART regimen.

### Cohort 2 Step 3 Entry Visit Procedures

| Administrative and Regulatory | • Complete final eligibility determination and confirmation*  
|                             | • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file |
| Behavioral and Counseling    | • Provide adherence counseling  
|                             | • Provide contraceptive counseling  
|                             | • Perform acceptability/tolerability assessment questionnaires |
| Clinical                    | • Update medical and medications history since last visit*  
|                             | • Perform symptom-directed physical exam*  
|                             | • Perform an ECG, if indicated* |
| Laboratory                  | Blood  
|                             | Collect blood for:  
|                             | • Hematology: complete blood counts, with platelets (cells/mm$^3$) and hemoglobin (g/dL)  
|                             | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m$^2$), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN)  
|                             | • CD4 count and percentage  
|                             | • HIV-1 RNA  
|                             | • Store plasma for genotypic and phenotypic resistance testing |
| Blood or Urine              | • For females, collect blood or urine for pregnancy test* |
| Study Product               | • Prescribe, dispense, and facilitate administration of oral study products, see Section 5.1 |

*Perform prior to enrollment

### 6.4.2 Cohort 2 Week 2 Visit (Step 3 – oral phase)

The Cohort 2 Week 2 visit is targeted to be conducted on day 14, counted from the day of entry, with a target window of +7 days from the target date, and an allowable window of +14 days from the target date.
PK samples will be collected at the Week 2 visit and over a maximum of a 7-hour period. The pre-dose PK sample collection should be performed prior to and on the same day as the oral study product dose observed at the site.

After the Entry visit and through the Week 2 visit, participants should be recommended to take the oral study product at the same time of day (morning or evening) as the Week 2 visit pre-dose PK collection time point. At minimum, for the three days prior to the Week 2 visit, participants should take their oral study product at the same time of day (morning or evening) as the scheduled pre-dose PK collection time point, and be fully adherent to their assigned daily oral study product regimen. In preparation for the Week 2 visit, sites may contact participants or parents and guardians, to reinforce adherence within the three days prior to the scheduled PK evaluation using retention methods as described in Section 4.8, as well as to remind the participant to hold the oral study product dose due on the day of the Week 2 visit. For example, sites may call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence.

If, for the three days prior to the Week 2 visit, either a missed dose is reported or the participant has not adjusted the timing of their oral study product dosing to align with the pre-dose PK collection time point, the Week 2 visit should be rescheduled. Additional guidelines for scheduling and conducting the Cohort 2 Week 2 visit are below.

- Participants and their parents/guardians should be reminded to hold administration of the daily oral study product due on the day of the Week 2 visit, to allow for a pre-dose PK sample collection and for the dose to be observed at the site. The Week 2 visit should be rescheduled if the oral study product dose was already taken and not observed at the site.
- Participants and their parents/guardians should also be reminded to return all oral study product at the Week 2 visit, such that the adherence assessment may be performed.
- Height and weight must be obtained on the same day as initiating the Week 2 PK evaluation.
- Participants should be provided food or a meal with the observed oral study product doses; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements.
- The oral study product dose dates, times, dose amounts, and food intake around the oral doses must be source documented and entered into eCRFs for the oral doses observed at the Week 2 visit in addition to the previous three doses.
- For participants who report intercurrent illness immediately prior to or on the day of the scheduled PK visit that may have interfered with study product administration or resulted in malabsorption of study product (e.g., fever, vomiting, diarrhea), the PK evaluation should be rescheduled.
- If the observed oral study product dose is not retained within 30 minutes (inclusive) of administration (e.g., the vomiting), the Week 2 visit should be rescheduled.
- Depending on site capacity and participant preferences, participants and their parents or guardians may stay at the clinical research facility overnight for the PK sampling.

Additional oral study product may be dispensed at this visit if needed to provide coverage until the Week 4a visit, per Section 5.1.3. Pregnancy test results must be obtained prior to any dispensing of additional oral study product.

Following the Week 2 visit, timing of taking the oral study product may be changed, if desired. However, participants should be encouraged to maintain the timing of taking their oral study product (morning or evening) through the Week 4b visit. Additional guidance regarding the
timing of oral study product dosing prior to the Week 2 visit is provided in the IMPAACT 2017 MOP.

<table>
<thead>
<tr>
<th>Cohort 2 Week 2 Visit Procedures (Step 3 – oral phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
</tr>
<tr>
<td>• Provide adherence counseling</td>
</tr>
<tr>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td>• Perform acceptability/tolerability assessment questionnaires, if indicated</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Update medical and medications history since last visit</td>
</tr>
<tr>
<td>• Perform symptom-directed physical exam (including height and weight)</td>
</tr>
<tr>
<td>• Perform adherence assessment</td>
</tr>
<tr>
<td>• Identify/review/update adverse events</td>
</tr>
<tr>
<td><strong>Laboratory Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)</td>
</tr>
<tr>
<td>• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)</td>
</tr>
<tr>
<td>• HIV-1 RNA</td>
</tr>
<tr>
<td>• Store plasma for genotypic and phenotypic resistance testing</td>
</tr>
<tr>
<td>• PK evaluation: Pre-dose and between 2-7 hours post-dose (2 PK collection timepoints)</td>
</tr>
<tr>
<td><strong>Blood or Urine</strong></td>
</tr>
<tr>
<td>• For females, collect blood or urine for pregnancy test; result must be obtained before observed dose of oral study product</td>
</tr>
<tr>
<td><strong>Study Product</strong></td>
</tr>
<tr>
<td>• Prescribe, dispense, and facilitate administration of the assigned oral study product, if indicated, see Section 5.1</td>
</tr>
</tbody>
</table>

6.4.3 Cohort 2 Week 4a Visit (Step 3 – oral phase)

The Cohort 2 Week 4a visit is targeted to be conducted on day 28, counted from the day of entry, with a target window of +7 days from the target date, and an allowable window of -7 days/+10 days from the target date.

Participants and their parents/guardians should also be reminded to return all oral study product at the Week 4a visit, such that the adherence assessment may be performed. Additional oral study products may be dispensed if needed to provide coverage until the Week 4b visit, per Section 5.1.3. Pregnancy test results must be obtained prior to any dispensing of additional oral study products.

Data collected through the Week 4a study visit will be assessed to determine eligibility to enter Step 4 and receive injectable CAB LA + RPV LA. Week 4a visit laboratory test results should be reviewed as soon as they are available, for determining Step 4 eligibility and scheduling the Week 4b visit. See Section 4.4 for Cohort 2 Step 4 eligibility criteria. Abnormal laboratory test result values from the Week 4a visit may be repeated prior to scheduling the Week 4b visit. If repeat laboratory test results confirm Step 4 eligibility, and all other eligibility criteria are met, the Week 4b visit may be scheduled within the target visit window (see Section 6.4.4 below) for Step 4 Entry and injectable study product administration, and may be combined with the Week 4a visit.

If Cohort 2 participants (who had not previously participated in Cohort 1 Step 2) are ineligible to receive injectable study product in Step 4, they will permanently discontinue oral study product use and complete an Early Termination visit 28 days after their last oral study product dose (see
Section 6.5.5. Cohort 1 Step 2 participants who continue in Cohort 2 Step 3, but are not eligible to progress to Cohort 2 Step 4 will be followed per the LSFU visit schedule (see Section 6.5).

<table>
<thead>
<tr>
<th>Cohort 2 Week 4a Visit Procedures (Step 3 – oral phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
</tr>
<tr>
<td>• Provide adherence counseling</td>
</tr>
<tr>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td>• Perform acceptability/tolerability assessment questionnaires, if indicated</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Update medical and medications history since last visit</td>
</tr>
<tr>
<td>• Perform complete physical exam</td>
</tr>
<tr>
<td>• Identify/review/update adverse events</td>
</tr>
<tr>
<td>• Perform adherence assessment</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td><strong>Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)</td>
</tr>
<tr>
<td>• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN)</td>
</tr>
<tr>
<td><strong>Blood or Urine</strong></td>
</tr>
<tr>
<td>• For females, collect blood or urine for pregnancy test; result must be obtained before dispensing oral study product, if dispensing is indicated at this visit</td>
</tr>
<tr>
<td><strong>Study product</strong></td>
</tr>
<tr>
<td>• Prescribe, dispense, and facilitate administration of oral study products, if indicated, see Section 5.1</td>
</tr>
</tbody>
</table>

6.4.4 Cohort 2 Week 4b Visit (Step 4 Entry – injection phase)

The Week 4b visit must take place after Week 4a laboratory test results are available, and with the target visit window of day 21-42, counted from the day of Step 3 entry. This visit should be scheduled to minimize the time between the Week 4a visit and initiation of the injectable study products in Step 4. Additionally, the Week 4b visit must occur within 42 days (inclusive) of Step 3 entry so as not to exceed the intended maximum of 6 weeks on oral study product.

Cohort 2 participants who meet eligibility criteria per Section 4.4. to progress to 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 study visit, which also serves as the Step 4 Entry visit. Note that HIV-1 RNA test results collected at the Week 4b visit are not required to be obtained or reviewed prior to administering injectable study product.

PK samples will be collected at the Week 4b visit. After the Week 2 visit and through the Week 4b visit, participants should be recommended to take the oral study product at the same time of day (morning or evening) as the Week 4b visit pre-dose PK collection time point. For the three days prior to the Week 4b visit, participants should ideally take their oral study product at the same time of day (morning or evening) as the scheduled pre-dose PK collection time point, and be fully adherent to their assigned daily oral study product regimen. However, the Week 4b visit may continue as scheduled if a missed dose is reported, or the participant has not adjusted the timing of their oral study product dosing to align with the pre-dose PK collection time point.

In preparation for the Week 4b visit, sites may contact participants or parents and guardians, to reinforce adherence and oral study product dose timing within the three days prior to the scheduled PK evaluation using retention methods as described in Section 4.8. For example, sites may call or visit the participant and/or parent/guardian prior to the scheduled PK evaluation to reinforce adherence. Participants and their parents/guardians should be reminded to hold administration of the daily oral study product due on the day of the Week 4b visit, to allow for a
pre-dose PK sample collection and for the dose to be observed at the site. Participants and their parents/guardians should also be reminded to return all oral study product at the Week 4b visit, such that the adherence assessment may be performed.

Prior to initiating the pre-dose PK sample collection, study staff should ascertain when the participant’s most recent oral study product dose was administered to determine whether oral study product should be administered during Week 4b visit:

- If the participant’s most recent oral study product dose was taken more than 12 hours from the Week 4b pre-dose PK sample collection, the pre-dose PK sample should be collected prior to observing the participant’s last oral study product dose administered (and observed) at the site. Sites should provide participants food or a meal with the observed oral study product dose; see Section 5.1 regarding RPV oral dosing regimen and food intake requirements.

- If the participant’s most recent oral study product dose was taken within 12 hours (inclusive) of the Week 4b pre-dose PK sample collection, an oral study product dose may not be administered during Week 4b visit. The Week 4b visit may still occur as scheduled and the pre-dose PK sample collection will be prior to the participant’s first study product injection.

The following Cohort 2 Week 4b visit procedures must be conducted on the same day (may not be conducted over a multi-day split visit) and as specified below:

- Contraceptive and adherence counseling must be provided prior to enrolling the participant into Step 4 to confirm the participant is willing to receive the injectable study product.
- Final eligibility determination and confirmation must be completed prior to completing the Step 4 eligibility checklist: medical and medications history, symptom-directed physical exam (must include height and weight), adherence assessment, and, for females, pregnancy testing; for females, pregnancy test results must be available for eligibility confirmation.
- The pre-dose PK sample must be collected prior to the participant’s first study product injection. See guidance above regarding whether the pre-dose PK sample is collected prior to an oral study product dose administered (and observed) at the site, or whether no oral study product dose is administered at this visit.
- The Step 4 paper-based eligibility checklist must be completed prior to enrolling the participant to Step 4.
- Enrollment to Step 4 must occur prior to prescribing the assigned injectable study product.
- Prescribing must occur prior to dispense assigned injectable study product.
- Administration of the assigned injectable study product must occur after enrollment into Step 4, and after prescribing and dispensing the participant’s assigned injectable study product.
- The post-dose PK sample must be collected after administration of both the oral study product and the injectable study product.

Note that acceptability and tolerability questionnaires must be administered relative to other Week 4b visit procedures as specified in the IMPAACT 2017 MOP. Visit procedures not otherwise specified may be conducted at any timepoint during the Week 4b visit. Operational guidance on the order of Week 4b visit procedures may be found in the IMPAACT 2017 MOP.
### Cohort 2 Week 4b Visit Procedures (Step 4 Entry - injection phase)

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
<td>• Provide contraceptive counseling*</td>
</tr>
<tr>
<td></td>
<td>• Provide adherence counseling*</td>
</tr>
<tr>
<td></td>
<td>• Perform acceptability/tolerability assessment questionnaires</td>
</tr>
<tr>
<td><strong>Administrative and Regulatory</strong></td>
<td>• Complete final eligibility confirmation for Step 4 Entry, see Section 4.4*</td>
</tr>
<tr>
<td></td>
<td>• Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant and generate SID; print and file a copy of the confirmation file</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>• Update medical and medications history since last visit*</td>
</tr>
<tr>
<td></td>
<td>• Perform symptom-directed physical exam*</td>
</tr>
<tr>
<td></td>
<td>• Identify/review/update adverse events*</td>
</tr>
<tr>
<td></td>
<td>• Perform adherence assessment*</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td><strong>Blood</strong> Collect blood for:</td>
</tr>
<tr>
<td></td>
<td>• HIV-1 RNA</td>
</tr>
<tr>
<td></td>
<td>• Store plasma for genotypic and phenotypic resistance testing</td>
</tr>
<tr>
<td></td>
<td>• PK evaluation: Pre-dose and 2 hours post-dose (2 PK collection timepoints), ± 30 minutes window is allowed for the 2-hours post-dose</td>
</tr>
<tr>
<td></td>
<td><strong>Blood or Urine</strong> For females, collect blood or urine for pregnancy test*</td>
</tr>
<tr>
<td><strong>Study product</strong></td>
<td>• Prescribe, prepare, and administer injectable study product, see Section 5.1</td>
</tr>
</tbody>
</table>

*Perform prior to completing the Step 4 eligibility checklist and prior to prescribing injectable study product.

#### 6.4.5 Cohort 2 Week 5 Visit (Step 4 – injection phase)

The Week 5 visit is targeted to be conducted 3 days after completion of the Week 4b Step 4 Entry visit (the first administration of injectable study product), with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

### Cohort 2 Week 5 Visit Procedures (Step 4 - injection phase)

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td></td>
<td>• Perform acceptability/tolerability assessment questionnaires, if indicated</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>• Update medical and medications history since last visit</td>
</tr>
<tr>
<td></td>
<td>• Perform symptom-directed physical exam</td>
</tr>
<tr>
<td></td>
<td>• Identify/review/update adverse events</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td><strong>Blood</strong> Collect blood for:</td>
</tr>
<tr>
<td></td>
<td>• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)</td>
</tr>
<tr>
<td></td>
<td>• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)</td>
</tr>
<tr>
<td></td>
<td>• PK evaluation: Single sample</td>
</tr>
</tbody>
</table>

#### 6.4.6 Cohort 2 Weeks 8 and 12 Visits (Step 4 – injection phase)

The Week 8 visit target date is 28 days after completion of the Week 4b visit, with a target window of -7 days/+3 days from the target date. The Week 12 visit target date is 56 days after completion of the Week 4b visit, with a target window of -7 days/+3 days from the target date.
Sites are expected to make every effort to schedule and conduct the injection study visits on the target visit date, or, when necessary, within the target visit window. If the participant is unable to come to the study visit and all scheduling options within the target visit window are exhausted, this visit may be conducted within the allowable window of ± 14 days from the respective target date and the CMC notified.

| **Behavioral and Counseling** | • Provide adherence counseling (Week 8 only)  
| | • Provide contraceptive counseling  
| | • Perform acceptability/tolerability assessment questionnaires |

### Clinical
- Update medical and medications history since last visit
- Perform symptom-directed physical exam
- Identify/review/update adverse events

### Laboratory Blood
- Collect blood for:
  - Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)
  - Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)
  - HIV-1 RNA
  - Store plasma for genotypic and phenotypic resistance testing
  - PK evaluation: Single pre-dose sample

### Blood or Urine
- For females, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product

### Study product
- Prescribe, prepare, and administer injectable study product, *see Section 5.1*

#### 6.4.7 Cohort 2 Weeks 16 and 20 Visits (Step 4 – injection phase)

The Week 16 visit target date is 84 days after completion of the Week 4b visit, with the Week 20 visit target date 112 days after completion of the Week 4b Step 4 Entry visit. Weeks 16 and 20 study visits each have a target window of ± 7 days, and allowable windows of ± 14 days from the respective target date. The CMC must be notified of a study product injection administered within the allowable window.
### Cohort 2 Weeks 16 and 20 Visit Procedures (Step 4 – injection phase)

| Behavioral and Counseling | • Provide contraceptive counseling  
• Perform acceptability/tolerability assessment questionnaires, *if indicated* |
|---------------------------|----------------------------------------------------------------------------------|
| Clinical                  | • Update medical and medications history since last visit  
• Perform symptom-directed physical exam  
• Identify/review/update adverse events |
| Laboratory Blood          | Collect blood for:  
• Hematology: complete blood counts, with platelets (cells/mm$^3$) and hemoglobin (g/dL)  
• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m$^2$), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
• HIV-1 RNA  
• Store plasma for genotypic and phenotypic resistance testing  
• PK evaluation: Single pre-dose sample |
| Blood or Urine            | • For females, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product |
| Study product             | • Prescribe, prepare, and administer injectable study product, *see Section 5.1* |

### 6.4.8 Cohort 2 Week 24 Visit (Step 4 – injection phase)

The Week 24 visit target date is 140 days after completion of the Week 4b visit, with a target window of ±7 days, and an allowable window of ± 14 days from the respective target date. The CMC must be notified of a study product injection administered within the allowable window.

### Cohort 2 Week 24 Visit Procedures (Step 4 – injection phase)

| Behavioral and Counseling | • Provide adherence counseling  
• Provide contraceptive counseling  
• Perform acceptability/tolerability assessment questionnaires  
• Conduct qualitative phone interview, *if indicated, see Section 11* |
|---------------------------|----------------------------------------------------------------------------------|
| Clinical                  | • Update medical and medications history since last visit  
• Perform complete physical exam  
• Identify/review/update adverse events  
• Sexual Maturity Rating assessment |
| Laboratory Blood          | Collect blood for:  
• Hematology: complete blood counts, with platelets (cells/mm$^3$) and hemoglobin (g/dL)  
• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m$^2$), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
• CD4 count and percentage  
• HIV-1 RNA  
• Store plasma for genotypic and phenotypic resistance testing  
• PK evaluation: Single pre-dose sample |
| Blood or Urine            | • For females, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product |
| Study product             | • Prescribe, prepare, and administer injectable study product, *see Section 5.1* |

### 6.4.9 Cohort 2 Week 25 Visit (Step 4 – injection phase)
The Week 25 visit is targeted to be conducted 3 days after completion of the Week 24 visit (the sixth administration of injectable study product), with a target window of +4 days from the target date, and an allowable window of -1 day/+5 days from the target date.

<table>
<thead>
<tr>
<th>Cohort 2 Week 25 Visit Procedures (Step 4 – injection phase)</th>
</tr>
</thead>
</table>
| **Behavioral and Counseling** | • Provide contraceptive counseling  
• Perform acceptability/tolerability assessment questionnaires, *if indicated*  
• Conduct qualitative phone interview, *if indicated, see Section 11* |
| **Clinical** | • Update medical and medications history since last visit  
• Perform symptom-directed physical exam  
• Identify/review/update adverse events |
| **Laboratory** | **Blood** | Collect blood for:  
• PK evaluation: Single sample |

6.4.10 **Cohort 2 Weeks 28, 32, 36, 40, 44, 48 Visits (Step 4 – injection phase)**

Weeks 28, 32, 36, 40, 44, and 48 study visits have the following target dates as counted from completion of the Week 4b visit:

- Week 28 visit target date is 168 days after Week 4b
- Week 32 visit target date is 196 days after Week 4b
- Week 36 visit target date is 224 days after Week 4b
- Week 40 visit target date is 252 days after Week 4b
- Week 44 visit target date is 280 days after Week 4b
- Week 48 visit target date is 308 days after Week 4b

The Weeks 28 through 48 study visits each have a target window of ±7 days, and allowable windows of ±14 days from the respective target date. The CMC must be notified of a study product injection administered within the allowable window.
### Cohort 2 Weeks 28, 32, 36, 40, 44, 48 Visit Procedures (Step 4 – injection phase)

| Behavioral and Counseling | • Provide contraceptive counseling  
|                          | • Provide adherence counseling (Week 48 only)  
|                          | • Perform acceptability/tolerability assessment questionnaires (Week 48 only; if indicated at all other visits)  
|                          | • Conduct qualitative phone interview, *if indicated, see Section 11*  
| Clinical                | • Update medical and medications history since last visit  
|                          | • Perform complete physical exam (Week 48 only)  
|                          | • Perform symptom-directed physical exam (Week 28 through Week 44 only)  
|                          | • Identify/review/update adverse events  
| Laboratory Blood | Collect blood for:  
|                          | • Hematology: complete blood counts, with platelets (cells/mm²) and hemoglobin (g/dL)  
|                          | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
|                          | • CD4 count and percentage (Week 48 only)  
|                          | • HIV-1 RNA  
|                          | • Store plasma for genotypic and phenotypic resistance testing  
|                          | • PK evaluation (Weeks 36 and 48 only): Single pre-dose sample  
| Blood or Urine | • For females, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product  
| Study product | • Prescribe, prepare, and administer injectable study product, *see Section 5.1*  

#### 6.4.11 Cohort 2 Weeks 52, 56, 64, 68, 76, 80, 88, 92 Visits (Step 4 – injection phase)

Cohort 2 Weeks 60, 72, 84 and 96 visits are further detailed in Section 6.4.12 below.

Weeks 52, 56, 64, 68, 76, 80, 88, and 92 study visits have the following target dates as counted from completion of the Week 4b visit:

- Week 52 visit target date is 336 days after Week 4b
- Week 56 visit target date is 364 days after Week 4b
- Week 64 visit target date is 420 days after Week 4b
- Week 68 visit target date is 448 days after Week 4b
- Week 76 visit target date is 504 days after Week 4b
- Week 80 visit target date is 532 days after Week 4b
- Week 88 visit target date is 588 days after Week 4b
- Week 92 visit target date is 616 days after Week 4b

These visits each have a target window of ±7 days, and allowable windows of ± 14 days from the respective target date. The CMC must be notified of a study product injection administered within the allowable window.
Cohort 2 Weeks 52, 56, 64, 68, 76, 80, 88, 92 Visit Procedures (Step 4 – injection phase)

| Behavioral and Counseling | • Provide contraceptive counseling  
|                          | • Perform acceptability/tolerability assessment questionnaires, if indicated  
|                          | • Conduct qualitative phone interview, if indicated, see Section 11  
| Clinical                 | • Update medical and medications history since last visit  
|                          | • Perform symptom-directed physical exam  
|                          | • Identify/review/update adverse events  
| Laboratory               | • For females, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product  
| Study product            | • Prescribe, prepare, and administer injectable study product, see Section 5.1  

6.4.12 Cohort 2 Weeks 60, 72, 84, 96 Visits (Step 4 – injection phase)

Weeks 60, 72, 84 and 96 study visits have the following target dates as counted from completion of the Week 4b visit:
- Week 60 visit target date is 392 days after Week 4b
- Week 72 visit target date is 476 days after Week 4b
- Week 84 visit target date is 560 days after Week 4b
- Week 96 visit target date is 644 days after Week 4b

These visits will each have a target window of ±7 days, and allowable windows of ± 14 days from the respective target date. The CMC must be notified of a study product injection administered within the allowable window.

At the Week 96 visit, Cohort 2 Step 4 participants may choose to continue to receive injectable CAB LA + RPV LA external to the protocol, and will exit the study. See Section 6.8 for more information on post-study contacts, and Section 14.11 for more information regarding post-trial access to study products. Participants who choose to discontinue receiving the injectable CAB LA + RPV LA beyond the Week 96 visit will not exit the study, and will be followed per the LSFU visit schedule as described in Section 6.5 below.
Cohort 2 Weeks 60, 72, 84, 96 Visit Procedures (Step 4 – injection phase)

| Behavioral and Counseling | • Provide contraceptive counseling  
• Provide adherence counseling (Weeks 72 and 96 only)  
• Provide instructions for cART administration and adherence counseling to the participant, parent or guardian, (Week 96 as study exit visit only)  
• Perform acceptability/tolerability assessment questionnaires (Week 96 only, if indicated at all other visits)  
• Conduct qualitative phone interview, if indicated, see Section 11 |
| Clinical | • Update medical and medications history since last visit  
• Perform complete physical exam (Week 96 only)  
• Perform symptom-directed physical exam (Weeks 60, 72, 84 only)  
• Identify/review/update adverse events  
• Sexual Maturity Rating assessment (Week 96 only) |
| Laboratory | Blood | Collect blood for:  
• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)  
• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
• CD4 count and percentage (Weeks 72 and 96 only)  
• HIV-1 RNA  
• Store plasma for genotypic and phenotypic resistance testing  
• PK evaluation: Single pre-dose sample |
| Blood or Urine | • For females, collect blood or urine for pregnancy test; result must be obtained before administering injectable study product |
| Study product | • Prescribe, prepare, and administer injectable study product, see Section 5.1 |

6.5 Long-Term Safety and Washout PK Follow-Up (LSFU) Visits

As noted in Section 3, the below specified participants will be followed according to the long-term safety and washout PK follow-up (LSFU) visit schedule:

- For Cohort 1 Step 2 participants: upon premature permanent discontinuation of injectable study product, or completion of the Cohort 1 Step 2 Week 16 visit

- For Cohort 1 Step 2 participants who enroll to Cohort 2 Step 3 but are ineligible for Step 4: upon premature permanent discontinuation of oral study product in Cohort 2 Step 3 (the LSFU visit schedule will be based on the date of their last study product injection, i.e. their Cohort 1 Step 2 Week 12 visit)

- For Cohort 2 Step 4 participants: upon premature permanent discontinuation of injectable study product, or completion of the Cohort 2 Step 4 Week 96 study visit but choosing to not continue to receive injectable CAB LA + RPV LA external to the protocol (see Section 6.4.12 above)

- Female participants who discontinue study product use (either oral or injectable study product) due to pregnancy during Steps 1-4

For participants permanently discontinuing injectable study product, the LSFU visit schedule is based on the date of the participant’s last study product injection. For Cohort 1 Step 2
participants who complete their Week 16 visit, their next scheduled visit will be the LSFU Week 12 Visit (and the LSFU Week 4 Visit is skipped).

Female participants who permanently discontinue study product (either oral or injectable study product and during Steps 1 through 4) due to pregnancy will be followed for 48 weeks, based on the date of the positive confirmatory pregnancy test result, per the LSFU visit schedule. For female participants who become pregnant during LSFU visits, the LSFU visits will continue as scheduled and not restart. All LSFU visit procedures will be conducted, with the exception that pregnancy testing will not be required for participants who are currently pregnant. See Section 8.3 for further details on management of pregnant participants and pregnancy outcome. Cohort 2 participants will resume (non-study provided) oral cART as soon as possible, and within 4 weeks of discontinuing study product. See the IMPAACT 2017 MOP for further guidance on scheduling LSFU study visits.

During LSFU, a single random PK sample will be collected at each visit as shown in the procedural tables below. Participants must have sufficient blood volume collection for their assigned study product(s), as specified in the LPC. See Section 6.16 for additional considerations for laboratory procedures, and Appendix I-C for blood volume ranges during LSFU visits.

6.5.1 LSFU Week 4 Visit

The LSFU Week 4 visit is targeted to be conducted 28 days after the last administration of injectable study product (or confirmatory positive pregnancy test result), with a target window of -14 days/+28 days from the target visit date. For Cohort 1 Step 2 participants completing the Week 16 visit, the LSFU Week 4 Visit will be skipped.

<table>
<thead>
<tr>
<th>LSFU Week 4 Visit Procedures (LSFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
</tr>
<tr>
<td>• Provide contraceptive counseling</td>
</tr>
<tr>
<td>• Provide adherence counseling</td>
</tr>
<tr>
<td>• Perform acceptability/tolerability assessment questionnaires</td>
</tr>
<tr>
<td>• Conduct qualitative phone interview, <em>if indicated</em>, see Section 11</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Update medical and medications history since last visit</td>
</tr>
<tr>
<td>• Perform complete physical exam</td>
</tr>
<tr>
<td>• Identify/review/update adverse events</td>
</tr>
<tr>
<td><strong>Laboratory Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)</td>
</tr>
<tr>
<td>• Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)</td>
</tr>
<tr>
<td>• HIV-1 RNA</td>
</tr>
<tr>
<td>• Store plasma for genotypic and phenotypic resistance testing</td>
</tr>
<tr>
<td>• PK evaluation: single sample</td>
</tr>
<tr>
<td><strong>Blood or Urine</strong></td>
</tr>
<tr>
<td>• For females, collect blood or urine for pregnancy test</td>
</tr>
</tbody>
</table>
6.5.2 LSFU Week 12 Visit

The LSFU Week 12 Visit is targeted to be conducted 84 days after the last administration of injectable study product (or confirmatory positive pregnancy test result), with a target window of -28 days/+42 days from the target visit date.

**LSFU Week 12 Visit Procedures (LSFU)**

| Behavioral and Counseling | • Provide contraceptive counseling  
|                           | • Conduct qualitative phone interview, *if indicated, see Section 11* |
| Clinical                  | • Update medical and medications history since last visit  
|                           | • Perform symptom-directed physical exam  
|                           | • Identify/review/update adverse events |
| Laboratory Blood          | Collect blood for:  
|                           | • Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)  
|                           | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
|                           | • HIV-1 RNA  
|                           | • Store plasma for genotypic and phenotypic resistance testing  
|                           | • PK evaluation: single sample |

**Blood or Urine** • For females, collect blood or urine for pregnancy test

6.5.3 LSFU Week 24 Visit

The LSFU Week 24 Visit is targeted to take place 168 days after the last administration of injectable study product (or confirmatory positive pregnancy test result), with a target window of ±42 days from the target visit date.

**LSFU Week 24 Visit Procedures (LSFU)**

| Behavioral and Counseling | • Provide contraceptive counseling  
|                           | • Conduct qualitative phone interview, *if indicated, see Section 11* |
| Clinical                  | • Update medical and medications history since last visit  
|                           | • Perform symptom-directed physical exam  
|                           | • Identify/review/update adverse events |
| Laboratory Blood          | Collect blood for:  
|                           | • Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)  
|                           | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)  
|                           | • HIV-1 RNA  
|                           | • Store plasma for genotypic and phenotypic resistance testing  
|                           | • PK evaluation: single sample |

**Blood or Urine** • For females, collect blood or urine for pregnancy test
6.5.4 LSFU Week 36 Visit

The LSFU Week 36 Visit is targeted to take place 252 days after the last administration of injectable study product (or confirmatory positive pregnancy test result), with a target window of ±42 days from the target visit date.

<table>
<thead>
<tr>
<th>LSFU Week 36 Visit Procedures (LSFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral and Counseling</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Laboratory Blood</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Blood or Urine</strong></td>
</tr>
</tbody>
</table>

6.5.5 LSFU Week 48 /Study Exit/Early Termination Visit

The LSFU Week 48 Visit is targeted to take place 336 days after the last administration of injectable study product (or confirmatory positive pregnancy test result), with a target window of ±42 days from the target visit date. These same visit procedures will be conducted as an Early Termination visit for participants withdrawing or terminating from the study prior to scheduled completion of study follow-up, instead of their regularly scheduled study visit, for a final series of evaluations. All participants completing this visit, whether as the LSFU Week 48 Visit (per the LSFU visit schedule) or as an Early Termination visit, will exit the study.

Scheduling and completion of Early Termination visits will be in consideration of participant withdrawal or termination; visit procedures may be combined with an ongoing study visit. Any procedures conducted within 14 days of an Early Termination visit need not be repeated, with the following target dates for completing the Early Termination visit:

- For Cohort 1 Step 1 and Cohort 2 Step 3 participants not progressing to the injection phase, an Early Termination visit is targeted to be completed 28 days after the participant’s last oral study product use; the Early Termination visit may be completed sooner, if necessary. For these participants, a PK evaluation will not be performed at this visit.

- For Cohort 1 Step 2, Cohort 2 Step 4, and any participant being followed per the LSFU visit schedule, an Early Termination visit is targeted to be completed within 28 days (inclusive) of the previous study visit.

Participants completing an Early Termination visit will be followed until resolution (return to baseline) or stabilization of any adverse events per Section 8.
Refer to Section 6.7 for the definition of scheduled completion of follow-up, and additional considerations for participants exiting the study (whether scheduled completion of follow-up or an early termination visit). Refer to Section 8.8 for criteria for participant withdrawal or premature termination from the study. The IMPAACT 2017 MOP provides further guidance on Early Termination visit scheduling considerations.

### LSFU Week 48 / Early Termination Visit Procedures

<table>
<thead>
<tr>
<th>Behavioral and Counseling</th>
<th>Blood, Laboratory</th>
</tr>
</thead>
</table>
| • Provide contraceptive counseling | Collect blood for:
| • Provide adherence counseling | • Hematology: complete blood counts, with platelets (cells/mm³) and hemoglobin (g/dL)
| • Perform acceptability/tolerability assessment questionnaires | • Chemistries: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m²), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (only if PK is also collected at this visit, g/dL)
| • Conduct qualitative phone interview, *if indicated, see Section 11* | • HIV-1 RNA
| | • Store plasma for genotypic and phenotypic resistance testing
| | • PK evaluation: single sample, (except Early Termination visit for Cohort 1 Step 1 and Cohort 2 Step 3 participants only)

<table>
<thead>
<tr>
<th>Behavioral and Counseling</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For females, collect blood or urine for pregnancy test</td>
<td></td>
</tr>
</tbody>
</table>

### 6.6 Confirmation of Virologic Failure Visit

Virologic failure is defined as two consecutive plasma HIV-1 RNA test results ≥200 copies/mL, from two separate specimens. Any participant with a plasma HIV-1 RNA level ≥200 copies/mL after enrollment should be recalled to the clinic for confirmatory testing 2-4 weeks after specimen collection for the initial test. Refer to Section 8.4 for more information on monitoring HIV-1 viral load, definitions of virologic failure, and managing virologic failure.

Scheduling of confirmatory testing should be in consideration of potential causes for virologic failure such as intercurrent illness, recent immunizations, inadequate adherence or interruptions to cART (for Cohort 1 or LSFU participants), interruptions of study product due to toxicity management, or other extenuating circumstances. For Cohort 1 Step 2 or Cohort 2 Step 4 participants (i.e. participants receiving injectable study product), confirmatory test results should ideally be obtained and reviewed prior to the next scheduled administration of injectable study product. While injection study visits for these participants may be delayed within the respective target visit window, injectable study product must not be withheld for pending confirmatory testing or results.

Confirmation of Virologic Failure visit procedures may be combined with regularly scheduled visit procedures if they are performed within the target window of a regularly scheduled visit. In
addition to the protocol-specific procedures listed in this section, study staff may complete other tasks and assessments consistent with local standards of care and site SOPs. Viral load results should be provided to participants and may be used to guide adherence counseling. See Section 6.14 for additional details on adherence counseling.

### Confirmation of Virologic Failure Visit Procedures

| Behavioral and Counseling | • Provide contraceptive counseling  
|                          | • Provide adherence counseling, if indicated  
|                          | • Provide instructions for cART administration and adherence counseling to the participant, parent or guardian, if indicated |
| Clinical                 | • Obtain interval medical and medications history  
|                          | • Perform symptom-directed physical exam  
|                          | • Identify/ review/ update adverse events  
|                          | • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) |
| Laboratory Blood         | Collect blood for:  
|                          | • HIV-1 RNA  
|                          | • Plasma for genotypic and phenotypic resistance testing  
|                          | • PK evaluation: single sample |
| Blood or Urine           | • For females, collect blood or urine for pregnancy test |

### 6.7 Study Exit

Participants may exit the study at different timepoints, with the following considered as scheduled study completion of follow-up:

- Upon permanently discontinuing injectable study product, Cohort 1 Step 2 and Cohort 2 Step 4 participants will be followed per the LSFU visit schedule, and will exit the study at their LSFU Week 48 study visit (see Section 6.5 above)

- Cohort 2 participants continuing to receive the study product after their Step 4 Week 96 visit (as external to the protocol; see Section 14.11) will not be followed per the LSFU visit schedule, and will exit the study at their Week 96 visit (See Section 6.4.12 above)

Any participant withdrawing or terminating from the study prior to these timepoints is considered as prematurely terminating from the study and the LSFU Week 48 study visit will be conducted as an Early Termination visit, instead of their regularly scheduled study visit, for a final series of evaluations. All visit procedures as described in and applicable to Section 6.5.5 will be completed for an Early Termination visit, with additional procedures and exceptions as noted.

At any study exit visit (scheduled completion of follow-up or an early termination visit), arrangements should be made to provide all clinically meaningful results to the participant and the participant’s parent or guardian. The participant and parent or guardian should be provided information on how to remain in contact with study staff (if desired) and how to learn about the results of the study when available. The participant and the participant’s parent or guardian should also be provided information, counseling, and referrals to non-study sources of care and treatment for the participant, as applicable. See Section 8.1 regarding management of adverse events at study exit, and Section 8.8 for additional considerations regarding participant withdrawal or termination.
6.8 Post-Study Contacts

Planning for transition to non-study care and treatment for participants exiting the study should begin prior to the participant’s scheduled study exit visit, and the transition should be implemented at the participant’s scheduled study exit visit. Study staff will complete a final study contact, with the participant and the participant’s parent or guardian, if applicable, within 4 weeks of the participant’s study exit visit to confirm the transition and should be documented in each participant’s study chart. These contacts are not expected to be entered into eCRFs. However, eCRF data collection is required after the participant’s study exit visit in the following scenarios:

- If a participant becomes pregnant while on study: Refer to Section 8.3; the pregnancy outcome must be ascertained and the relevant eCRFs entered after the participant exits the study to record the pregnancy outcome.

- If confirmation of virologic failure is pending after the LSFU Week 48 visit: Refer to Section 6.5; in this scenario, the confirmatory HIV-1 RNA PCR assay must be performed and the relevant eCRFs entered to record the result of the assay.

- If the participant has any Grade 3 or higher adverse event at the study exit visit: participants should be asked to be continued on study for up to 28 days or until resolution (return to baseline) or stabilization (i.e. Grade 2 or lower), whichever is sooner, with the frequency of visits determined by the site investigator.

6.9 Procedures for Continued Oral and Injectable Study Product Administration

The following procedures must be performed on the same day as and prior to administering study product (i.e. either dispensing oral study product or administering study product injection), to assess for any indication of study product hold or permanent discontinuation:

- Clinical evaluations per the respective scheduled study visit (see Section 6 and Appendix I)
- Laboratory test results from the previous study visit obtained and reviewed for indication of study product hold or permanent discontinuation (see Section 8)
- For females, a negative pregnancy test result
- For females of childbearing potential, confirmation (per participant report) of effective contraception, per Section 6.13

See Section 8.1 for details regarding participant management. See Section 8.6 for details regarding deferring study product due to managing adverse events and other indications.

6.10 Medical and Medications History

Collection of medical and medication history information is required at each scheduled visit. A baseline history is established at Screening and Entry, and interval (since the last visit) histories are obtained at subsequent follow-up visits. All history information may be obtained based on participant self-report or as reported by the parent or guardian but available medical records should be obtained when possible to supplement self-reported information. Refer to the IMPAACT 2017 MOP for additional guidance regarding establishing baseline history.

Documented medical conditions will be assessed for severity as described in Section 7.3.3, and new conditions occurring during follow-up will also be assessed for relationship to study product
as described in Section 8.1. Relevant dates will be recorded for all conditions and medications; see Section 5.6 for more information on concomitant medications.

Table 7 specifies the baseline and interval medical and medications history elements that must be source documented for participants, as well as associated eCRF entry requirements.

**Table 7. Documentation Requirements for Medical and Medication Histories**

<table>
<thead>
<tr>
<th>Assess for and Source Document</th>
<th>Enter into eCRFs or SES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Medical and Medication History Elements</strong></td>
<td></td>
</tr>
<tr>
<td>Age, sex at birth, and other socio-demographics</td>
<td>Yes (all)</td>
</tr>
<tr>
<td>HIV diagnosis, mode of transmission, and ARV treatment history (including all prior ARV use)</td>
<td>Yes (all, including start/stop dates, dates and values of results, as applicable)</td>
</tr>
<tr>
<td>History of allergy and/or hypersensitivity (including to ARVs)</td>
<td>Yes (all)</td>
</tr>
<tr>
<td>Medical conditions (including malignancies) occurring during the 28 days prior to entry, ongoing at entry, as well as all prior significant central nervous system disorders (including seizures and migraines/headaches), mood disorders (such as depression), and significant liver disease resulting in hospitalization or interfering with daily activities.</td>
<td>Yes (all, including start/stop dates, and dates of diagnosis, as applicable)</td>
</tr>
<tr>
<td>Medications, (other than ARVs, see above) taken within the 28 days prior to enrollment and/or ongoing at enrollment</td>
<td>Yes (all, except herbal or traditional medications are not be captured on eCRFs)</td>
</tr>
<tr>
<td>Assessment of sexual activity</td>
<td>Yes</td>
</tr>
<tr>
<td>Contraceptives ongoing at enrollment, including start date and most recent date of administration of current contraceptive method.</td>
<td>Yes</td>
</tr>
<tr>
<td>Note: Hormonal-based contraceptives must have been initiated within the prescribed time, per the respective contraceptive method, to be considered effective at the time of Entry. The site IoR or designee is responsible for ensuring that the contraceptive is used in accordance with the approved product label</td>
<td></td>
</tr>
<tr>
<td>Any other information needed to determine eligibility for the study</td>
<td>—</td>
</tr>
<tr>
<td><strong>Interval Medical and Medication History Elements</strong></td>
<td></td>
</tr>
<tr>
<td>Current status of conditions that were ongoing at the previous visit</td>
<td>Any updates of previous entries (e.g., resolution dates)</td>
</tr>
<tr>
<td>Occurrence of any new conditions since the last visit</td>
<td>Any newly identified adverse events that meet criteria in Section 7.2</td>
</tr>
</tbody>
</table>
### Assess for and Source Document

<table>
<thead>
<tr>
<th>Assess for and Source Document</th>
<th>Enter into eCRFs or SES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current status of medications (including contraceptives) that were ongoing at the previous visit</td>
<td>Any updates of previous entries (e.g., stop dates)</td>
</tr>
</tbody>
</table>
| Use of any new medications since the last visit (see Section 5.6 for more information on concomitant medications) | • Any concomitant ARVs taken  
• Any new use of concomitant medications, including contraceptives  
• All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2 |
| Note: For participants in Cohort 1 and LSFU, ARVs would be considered concomitant medications. | Note: herbal or traditional medications taken during follow-up should not be captured on eCRFs. |
| Oral Study Product since the last visit (for Cohort 1 Step 1, Cohort 2 Step 3 participants, and any Cohort 1 or Cohort 2 participants on oral bridging) | • Oral study product doses taken from time of enrollment through completion of follow-up |
| **Note:** Injectable study product information is not considered as part of medical and medications history since last visit, and will be collected as per Section 5. See Section 6 above for details regarding study product dosing documentation requirements for PK evaluations. | |
| Assessment of sexual activity since the last visit | — |

#### 6.11 Physical Examinations

A physical examination is required at each scheduled visit, either as a complete physical exam or as a symptom-directed physical exam, per the specified procedures for each visit. Table 8 below outlines the visits when a complete physical exam is required; symptom-directed exams are required at all other scheduled visits.

<table>
<thead>
<tr>
<th>Table 8. Visits Requiring Complete Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
</tr>
<tr>
<td><strong>Cohort 2</strong></td>
</tr>
<tr>
<td><strong>LSFU</strong></td>
</tr>
</tbody>
</table>

Complete exams should include the following:  
• Height and weight  
• Vital signs, including heart rate, temperature and blood pressure  
• Examination of:  
  – General appearance  
  – Head  
  – Eyes
- Ears
- Nose
- Neck
- Mouth and throat
- Lymph nodes
- Lungs
- Heart
- Abdomen
- Musculoskeletal system
- Skin
- Neuro
- Sexual Maturity Rating (SMR) (at Screening for both Cohort 1 and Cohort 2, Cohort 1 Week 16, Cohort 2 Week 24, and LSFU Week 48 visits)

- Examination of other body systems driven by other identified signs or symptoms

Symptom-directed exam should include the following:
- Height and weight
- Vital signs, including heart rate, temperature and blood pressure
- Examination of body systems driven by identified signs or symptoms

At all visits, additional assessments may be performed at the discretion of the examining site investigator. All exam findings should be source documented, with vital signs and any abnormal findings entered into eCRFs, as specified in Section 7.2. Additionally, height and weight must be obtained on the same day as any PK sample collection, and source documented and entered into eCRFs, even if a physical exam was already conducted as part of that visit.

6.12 Performing an Electrocardiogram (ECG/EKG)

Electrocardiogram (ECG) readings are required at Screening (for both Cohort 1 and Cohort 2), Cohort 1 Week 13, and Cohort 1 Week 16. For all ECG readings, a 12-lead ECG should be performed with the participant in a semi-supine position. An ECG machine that automatically calculates the heart rate and measures QTc intervals is preferred, and the automated calculations can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results.

At the Cohort 1 Screening and Cohort 2 Screening visits, the ECG reading should be done in triplicate such that three, single automated QTc readings will be done, each separated by at least 2 minutes, with the mean value establishing baseline. The triplicate ECG reading must be conducted within 2 weeks (14 days) of the participant’s Entry visit; the triplicate ECG conducted at the Screening may be repeated to maintain this timeframe. During follow-up, single automated readings will be compared to the baseline value, with a result of > 500 msec requiring a repeat reading in triplicate (as performed at the respective Screening visit). See Section 8.2 for Monitoring and Management of QTc Prolongation.

All ECG readings should be source documented, and baseline (i.e. mean value of triplicate readings) and follow-up values entered into eCRFs. Abnormal findings identified after administration of first dose of oral study product will be entered into eCRFs as specified in Section 7.2.
6.13 Pregnancy Testing and Contraceptive Counseling

Pregnancy testing is required for all female participants, at specified study visits and prior to administration of study product, regardless of self-reported sexual activity or childbearing potential. See Section 8.3 for details on participant and study product management relating to Management of Contraception and Pregnancy.

As stated in Section 4.1.15, females of childbearing potential are required to use at least one of the allowable effective method of contraception to enroll to the study. For any female participant who becomes of childbearing potential during the study, an allowable effective contraceptive method must be initiated prior to administration of study product (oral or injectable study product). A female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. Women are considered to be in a postmenopausal state when they are > 54 years of age with cessation of previously occurring menses for > 12 months without an alternative cause. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

The effective methods of contraception allowed for this study are listed below.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject’s preferred and usual lifestyle

OR

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of < 1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of < 1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

OR

- Consistent and correct use of one hormonal method AND one barrier method
  - Barrier methods
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Male condom (with or without spermicide)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

For any methods of contraception not included in the listing which have a < 1% failure rate, per the product label, may be allowed in consultation with the CMC.
Study staff will provide contraception counseling to all male and female participants, regardless of self-reported sexual activity or childbearing potential, at all study visits. Counseling will include maintaining contraceptive use for 30 days after the last oral study product use and for 48 weeks after any single injection of study product. Female participants should also be encouraged to delay pregnancy for at least 30 days following oral study product use, or 48 weeks following any single injection of study product.

At any point during study participation, additional counseling on correct use of chosen contraceptive methods should also be offered according to site SOPs; this will include information on correct use of barrier methods. For Cohort 1 and all LSFU participants, contraceptive counseling will also reflect the ARVs which participants are currently taking for the potential interactions between these ARVs and available contraceptive methods. Contraceptive counseling may be tailored to be age-appropriate, and will be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Study sites should ideally integrate provision of contraceptive methods with other services offered to study participants, and should provide referrals to non-study sources of methods that cannot be provided at the study site. Study staff should confirm (per participant report) effective contraception with one of the study required contraceptive methods at each visit in which study product is administered.

Pregnancy test results will be disclosed to participants and their parent/guardians consistent with local standards of care; local standard procedures will be noted in site-specific informed consent and assent forms.

### 6.14 Study Product Adherence Assessment and Adherence Counseling (Study Product, cART Regimen, Study Visits)

Prior to progressing to the injection phase, participants should be assessed for adherence to oral study product and whether sufficient evaluations of safety and tolerability were permitted to be conducted during the oral lead-in phase. Pill counts will be conducted at the Week 2, Week 4a and Week 4b visits, but will not be used as a basis for counseling participants on oral study product adherence. Information obtained through the pill counts, participant self-report, and adherence counseling discussions should be used in combination as a broader adherence assessment evaluation when assessing each participant for eligibility to receive injectable study product. The IoR, or designee, should source document all contributing information leading to and final determination of Step 2 or Step 4 eligibility with regards to Sections 4.3.4 and 4.4.4.

Adherence counseling will be provided to all study participants and parents/guardians throughout study participation at specified study visits, and as needed based on IoR discretion. Topics discussed during adherence counseling will vary depending on the Cohort, Step and whether participants are also taking a (non-study provided) cART regimen:

- For Cohort 1 participants, adhering to the (non-study provided) cART regimen and instructions on cART administration will be provided. These topics will also be discussed prior to participants transitioning to the LSFU visit schedule (if permanently discontinuing injectable study product), during specified LSFU visits, and at Early Termination visits.
- For Cohort 1 Step 1 and Cohort 2 Step 3 participants, counseling on adhering to the oral study product will be provided in relation to the purpose of the oral lead-in phase and allowing for sufficient evaluations of safety and tolerability.
• For Cohort 1 Step 2 and Cohort 2 Step 4 participants, counseling will include discussion with participants regarding the importance of adhering to the intended injectable study product dosing regimen, and adhering to the study visit schedule.
• For all Cohort 2 participants, counseling will include discussion on the importance of adhering to the study visit schedule as these participants are no longer receiving a (non-study provided) cART regimen.
• For participants exiting the study at the Cohort 2 Week 96 visit (to continue injectable CAB LA + RPV LA external to the protocol), counseling will include the importance of adhering to the intended injectable dosing regimen and schedule.

Counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Counseling should be provided in a client-centered manner, tailored as needed to the information, skills building, and support needs of each participant. Information on correct use of oral study products will be provided. Counseling will also address challenges to consistent use of oral study product or attending injectable study visits over time, with the aim of supporting participants in identifying strategies to address any such challenges.

6.15 Acceptability and Tolerability Assessments

Acceptability and tolerability of the study products will be assessed at specified study visits, and at visits during which permanent study product discontinuation is initiated. These assessments will be administered to participants by site staff via questionnaires covering topics on participant perceptions of the study product injections, reasons for switching from daily oral cART to long-acting study products, satisfaction with treatment, quality of life, and treatment preferences. Prior to the participant leaving the clinic, questionnaires should be reviewed and any potential adverse events reported in the participant’s responses should be clinically assessed. Further guidance and considerations for conducting and reviewing the acceptability and tolerability assessments, the timing of administering the assessments relative to other visit procedures, as well as guidance regarding the appropriate site staff to administer specified assessments is provided in the study-specific MOP.

6.16 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management.

6.16.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the LPC, which will be posted on the study-specific webpage: http://impaactnetwork.org/studies/IMPAACT2017.asp. Site staff collecting specimens for PK evaluations must prepare the workspace and supplies with regards to protecting all specimens from light, as specified in the LPC.

In accordance with US NIH recommendations, pediatric (less than 18 years) blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg over any eight-week period. Adult (18 years and older) blood collection will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.
In the event blood collection must be limited, available specimens will be prioritized for use in the following order: (1) safety (chemistries, hematology, pregnancy testing), (2) PK, (3) HIV-1 viral load, and (4) genotypic resistance storage sample.

6.16.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced above, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedules of Evaluations in Appendix I-A, Appendix I-B, and Appendix I-C and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC. Any specimens stored at the Screening Visit for participants who do not subsequently enroll in the study will be destroyed.

The following will be performed in real time at local CLIA-certified laboratories:

- Pregnancy tests
- Hematology laboratory testing: complete blood counts, with platelets (cells/mm3) and hemoglobin (g/dL)
- Chemistry laboratory testing: Creatinine, Creatine kinase, Creatinine Clearance (CrCl; Schwartz formula mL/min/1.73m2), Total bilirubin, ALT (u/l), Lipase (u/l), Blood Urea Nitrogen (BUN), Albumin (g/dL)
- CD4 count and percentage tests
- Plasma HIV-1 RNA assays

HIV-1 RNA assays must be performed in real time in a CLIA-certified (US sites) laboratory using the testing platform specified in the LPC.

HIV genotypic and phenotypic resistance samples collected at the Confirmation of Virologic Failure visit must be processed with plasma retained at the site laboratory, as specified in the LPC, pending HIV-1 RNA test results to confirm virologic failure. For participants with confirmed virologic failure, aliquots of plasma stored for resistance testing at the Confirmation of Virologic Failure visit and other study visits as requested by the Clinical Management Committee (CMC), will be shipped with testing performed in real time at a designated CLIA-certified testing laboratory, as specified in the LPC. If failure is not confirmed, resistance samples collected at the Confirmation of Virologic Failure will remain stored at the site laboratory.

HIV genotypic and phenotypic resistance samples for storage (collected at study visits other than the Confirmation of Virologic Failure visit) must be processed, and stored per the LPC; these samples will be shipped to a designated CLIA-certified testing laboratory for testing as requested by the CMC.

Specimens collected, processed, and stored at site laboratories for PK evaluations are generally expected to be shipped to the designated testing laboratory as follows, with more frequent shipping as requested by the protocol team:

- Cohort 1 PK samples should be shipped in real time upon completion of the Week 2 visit, and PK samples from Week 4b through Week 16 should be shipped upon completion of the Week 16 visit.
• Cohort 2 (Week 2 through Week 48 visits) and LSFU PK samples will be batched and shipped on a quarterly basis.
• Cohort 2 (Weeks 60, 72, 84, 96 visits) and Confirmation of Virologic Failure visit PK samples will be batched and shipped upon request by the protocol team.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Participants and participants’ parents or guardians (if applicable) will be asked to provide written informed consent/assent for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies. Parents or guardians (or participants) may choose to provide or to decline informed consent for future research use of residual specimens with no impact on other aspects of participation in the study. If informed consent for future research use of residual specimens is initially provided but if participants’ parents or guardians (or participants) subsequently change their mind and withdraw that consent, all remaining residual samples will be destroyed.

6.16.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the Clinical Management Committee (CMC) and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in Section 7.1 and described in greater detail in Sections 9.5.1 and 9.5.2.

Unless otherwise noted, the specifications of this section only apply to adolescent participants in Cohort 1, Cohort 2, and LSFU.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the CMC if unexpected concerns arise. Site investigators will enter safety-related data into eCRFs as indicated in Section 7.2 and complete expedited adverse event (EAE) reporting as indicated in Section 7.3. Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to any study participants or others.
Importantly, site investigators must inform the CMC of any of the following:

- New onset seizure
- Grade 3 or higher creatine kinase, total bilirubin (unless isolated atazanavir related hyperbilirubenemia with normal direct bilirubin), or lipase
- Grade 3 or higher adverse events assessed as related to study product
- For Cohort 1, Step 2 and Cohort 2, Step 4 participants, a missed scheduled study product injection visit

For creatine kinase, total bilirubin and lipase elevations, and Grade 3 or higher adverse events assessed as related to study product, the CMC should be informed as soon as possible and within 48 hours of awareness of the event. For new onset of seizure, the CMC should be informed within 24 hours of awareness of the event.

For Cohort 1, Step 2 and Cohort 2, Step 4 participants who miss a scheduled study product injection, or who have a temporary hold which will cause the participant to miss a scheduled study product injection, the CMC should be consulted as soon as possible and within 48 hours of site awareness.

7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Co-Chairs, Medical Officers, Statisticians, Data Managers, Clinical Trial Specialists, protocol Pharmacologists, at least one protocol Investigator, and at least one medical representative from Viiv and Janssen. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility, management of adverse events, study product administration, cART regimens, and other concomitant medications. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the CMC will monitor participant safety through routine review of study data reports as described in Section 9.5.1.

Detailed toxicity management algorithms including criteria for discontinuation of study product can be found in Section 8 below.

7.1.3 Study Monitoring Committee (SMC)

An independent IMPAACT Study Monitoring Committee (SMC) will monitor participant safety through routine and as needed reviews of study data. Refer to Section 9.5.2 for more information on the composition and role of the SMC in monitoring of this study.

7.2 Safety-Related Data Collection

This section describes eCRF data collection for pre-existing conditions and adverse events. Criteria for expedited reporting of specified adverse events are further detailed refer in Sections 7.3.2 and 7.3.3 below.

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied only to the adolescent participants, beginning at the time of enrollment (as defined in Section 4.7), regardless of subsequent administration of or exposure to study
product. Any untoward medical conditions (including abnormal laboratory test results, signs, symptoms, or diseases) identified prior to enrollment will be considered pre-existing conditions.

**Pre-Existing Conditions**

The following pre-existing conditions will be entered into medical history eCRFs:

- All conditions identified during the 28 days prior to study entry
- All conditions ongoing at the time of enrollment
- All prior significant central nervous system disorders (including seizures and migraines/headaches), mood disorders (such as depression), and significant liver disease resulting in hospitalization or interfering with daily activities

**Adverse Events**

The following adverse events will be entered into the adverse events eCRFs:

- Grade 1 and higher clinical adverse events (including all signs, symptoms, and associated laboratory test results of the clinical adverse event)
- Grade 3 or higher laboratory-only adverse events
- All adverse events that result in temporary study product hold or permanent discontinuation of study product
- All adverse events that meet criteria for expedited reporting per protocol Section 7.3.2

**Laboratory Test Results**

All protocol-required laboratory test results will be entered into laboratory eCRFs.

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 EAE Reporting to DAIDS


The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.
7.3.2 EAE Reporting Requirements for this Study

The SAE (serious adverse event) reporting category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. In addition, the following must also be reported in an expedited manner (i.e., as EAEs), regardless of severity or relationship to study product:

- ALT $\geq 3x$ ULN with total bilirubin $\geq 2x$ ULN
- ALT $\geq 8x$ ULN
- ALT $\geq 3x$ baseline ALT with signs/symptoms of acute hepatitis
- ALT $\geq 5x$ ULN that persists $>2$ weeks
- Any seizure event

The study agents for which expedited reporting are required are: oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), and oral rilpivirine (RPV), and long-acting injectable rilpivirine (RPV LA).

Information on AEs will be included in reports to the US FDA, and other government and regulatory authorities, as applicable.

7.3.3 Grading Severity of Events (applies to EAEs and all other adverse events)

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 http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

7.3.4 EAE Reporting Period

The EAE reporting period for this study is the protocol-specific period of follow-up, beginning at the time of study entry and ending on the date of the final follow-up visit. For all participants who continue per the LSFU visit schedule, EAE reporting requirements continue throughout LSFU follow-up. For Cohort 1 participants who may enter Cohort 2 after having exited the study, EAE reporting requirements resume upon re-entry into the study.

After this reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).
8 PARTICIPANT MANAGEMENT

8.1 Management of Adverse Events

All adverse events identified in this study will be source documented in participant research records, consistent with the policies and procedures referenced in Section 12. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3) and its relationship to study product, assessed by the site clinician according to the following categories and definitions:

**Related**
There is a reasonable possibility that the adverse event may be related to the study agents: oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), and oral rilpivirine (RPV), and long-acting injectable rilpivirine (RPV LA)

**Not related**
There is not a reasonable possibility that the adverse event may be related to the study agents: oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), and oral rilpivirine (RPV), and long-acting injectable rilpivirine (RPV LA)

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in Section 7.3.1 above.

Adverse events identified in enrolled participants will be managed based on their severity and assessed relationship to study product, as described in greater detail below. Unless otherwise specified below, AEs (clinical as well as abnormal laboratory values) should be managed per general management guidelines in Section 8.1.1.

Individual dose adjustments or reductions of study products for management of toxicity-related AEs are not allowed. For Cohort 2 participants, in the event of a temporary study product hold or a permanent discontinuation of study product, both study products will always be held (or discontinued). For additional considerations regarding Cohort 2 participants and resuming (non-study provided) cART, see Section 8.6 regarding temporary product holds, and Section 8.7 regarding permanent discontinuation of study product.

All adverse events must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event. Additional evaluations beyond those listed in the Schedules of Evaluations (see Appendix I) may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study product. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

Adverse events that are ongoing at the time of the final study visit, particularly those of Grade 3 or higher severity, should generally be followed to resolution or stabilization by the site investigator; if this is not possible, the site investigator should actively facilitate referral to local non-study sources of appropriate medical care and treatment. Unless otherwise specified, when management of an adverse event requires consultation with the CMC, the CMC should be contacted as soon as possible and within two business days of site awareness of the event.
8.1.1 General Management of Adverse Events

Sections 8.1.2–8.1.9 provide detailed participant and study product management on specified adverse events and abnormal laboratory test result values. If an observed adverse event or abnormal laboratory test result value is not listed in those sections below, the guidance in this section (General Management of Adverse Events) should be followed.

In general, the IoR or designee has the discretion to temporarily hold study product at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. See Sections 8.6 and 8.7 below.

- **Grade 1 or Grade 2, regardless of relationship to study product:** continue study product, and manage participant according to standard of care practice at the site.

- **Grade 3 assessed as not related:** continue study product, and re-evaluate participant at least weekly until improvement to Grade 2 or lower. If improvement to Grade 2 or lower cannot be documented in 2 weeks, consult the CMC.

- **Grade 3 assessed as related:** temporarily hold study product use, notify the CMC, and re-evaluate the participant at least weekly until improvement to Grade 2 or lower. If within 2 weeks the AE has improved to Grade 2 or lower, study product may be resumed. Consult the CMC if improvement to Grade 2 or lower cannot be documented within 2 weeks.
  - If study product use is resumed and the same Grade 3 AE deemed related to study product, recurs at any time, the IoR/designee must temporarily hold study product and consult the CMC for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the study product.

- **Grade 4 regardless of relationship to study product:** temporarily hold study product, re-evaluate the participant as soon as possible or within 2 business days, and consult the CMC. Continue the temporary product hold until a recommendation is obtained from the CMC.

8.1.2 Injection Site Reactions (ISRs)

An ISR is defined as an adverse event which, in the opinion of the IoR or designee, results in pain out of proportion of what would be expected when a person gets an intramuscular injection, tenderness, erythema, redness, induration or swelling, or pruritis, regardless of when it occurs after administration of an injection. ISRs should be assessed and reported per the Site Reactions to Injections and Infusions section of the DAIDS toxicity tables.

Participants with ISRs should be managed as follows, regardless of relationship to study product:

- **Grade 1 or Grade 2:** continue study product, and manage the participant symptomatically (e.g. cold/warm compress, acetaminophen, ibuprofen)

- **Grade 3 or 4:** consult the CMC to determine etiology and study product management
8.1.3 Creatine Kinase (CK/CPK) Elevation

All participants with elevated CPK results from baseline should be assessed for a history of use of drugs known to cause increase of CPK (such as statins), and/or physical activity or exercise preceding the CPK sample collection. Participants should abstain from exercise for more than 24 hours and be well hydrated prior to any repeat sample collection.

- **Grade 1 or 2:** continue study product.

- **Grade 3:** continue study product and repeat testing from a new sample within 14 days. If the repeat test result is Grade 3 or higher, consult the CMC within 48 hours.

- **Grade 4, with no signs/symptoms of rhabdomyolysis:** continue study product and repeat testing from a new sample within 7 days, and after the participant has abstained from exercise for >24 hours. If the repeat test result is Grade 2 or lower, manage per grade. If the repeat test result is Grade 3 or higher, consult the CMC within 48 hours for further guidance on study product and participant management.

- **Grade 4, with signs/symptoms of rhabdomyolysis:** For Grade 4 CPK elevations that are in the opinion of the IoR associated with signs/symptoms of rhabdomyolysis (such as myalgias, muscle pain, dark urine, or clinically significant changes in creatinine clearance), temporarily hold study product, repeat testing from a new sample within 7 days, and consult the CMC within 48 hours for further guidance on study product and participant management.

8.1.4 Lipase Elevations and Pancreatitis

Participants with asymptomatic elevations in lipase should be managed as follows, regardless of relationship to study product:

- **Grade 1 or 2:** continue study product, and be followed for development of symptoms (i.e. pancreatitis) according to standard of care practice at the site.

- **Grade 3 or higher:** temporarily hold study product, and repeat testing on a newly obtained sample within 2 weeks. If the repeat test result is Grade 2 or lower, resume study product. If upon resuming study product lipase elevation is Grade 3 or higher, permanently discontinue study product. If the repeat test result is Grade 3 or higher, and in the absence of other diagnoses, permanently discontinue study product.

Participants with a confirmed diagnosis of clinical pancreatitis (i.e. symptomatic elevations in lipase) should be managed as follows:

- **Grade 2 or higher assessed as not related:** temporarily hold study product, notify the CMC within 48 hours, and re-evaluate the participant weekly until complete resolution (i.e. return to baseline). Upon returning to baseline, resume study product and re-evaluate the participant every 2 weeks for at least 6 weeks. If after resuming study product, any elevation of lipase of Grade 2 or higher, or any recurrence of symptoms, the permanently discontinue study product.

- **Grade 2 or higher assessed as related:** permanently discontinue study product, and notify the CMC.
8.1.5 Elevations in ALT, Bilirubin

This section provides guidance on study product and participant management due to elevations in ALT, including considerations of accompanying bilirubin test results. Participants with an abnormal total bilirubin test result should have serum bilirubin fractionation (i.e. direct bilirubin) testing requested, if available, with confirmatory repeat testing, at the timepoints indicated below.

In all cases of elevated ALT and/or elevated bilirubin (total or direct), possible alternative etiology should be assessed and the underlying illness treated, or the likely causative agent removed.

As noted in Section 7.1.1, the CMC must be informed of any Grade 3 or higher total bilirubin, unless isolated atazanavir related hyperbilirubenemia with normal direct bilirubin. Asymptomatic Cohort 1 participants on an Atazanavir-containing cART regimen, who present with hyperbilirubinemia (any grade) with a normal direct bilirubin, normal ALT, and no other alternate etiology for the unconjugated hyperbilirubinemia, may continue study product use in consultation with the CMC.

<table>
<thead>
<tr>
<th>ALT SEVERITY GRADE WITH ACCOMPANYING BILIRUBIN SEVERITY GRADE (TOTAL OR DIRECT)</th>
<th>PARTICIPANT AND STUDY PRODUCT MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 ALT, and/or Grade 1 bilirubin</td>
<td>Continue study product use, and repeat testing at the next scheduled study visit, or more frequently at the discretion of site investigator.</td>
</tr>
<tr>
<td>ALT SEVERITY GRADE WITH ACCOMPANYING BILIRUBIN SEVERITY GRADE (TOTAL OR DIRECT)</td>
<td>PARTICIPANT AND STUDY PRODUCT MANAGEMENT</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Grade 2 ALT</strong></td>
<td>• With ≤ Grade 1 bilirubin (at the Week 4a visit): Continue study product use, and repeat testing within 72 hours. If repeat test results return to baseline, continue per study visit schedule (see Sections 6.3.3, and 6.4.3). If repeat test results in Grade 2, consult the CMC immediately and manage per CMC guidance.</td>
</tr>
<tr>
<td></td>
<td>• With ≤ Grade 1 bilirubin (all visits except the Week 4a visit): Continue study product use, and repeat testing weekly. If still Grade 2 ALT after 4 weeks, consult the CMC.</td>
</tr>
<tr>
<td></td>
<td>• With Grade 2 or higher bilirubin: Hold study product, and repeat testing weekly. If repeat test results of both ALT and bilirubin return to baseline, resume study product use, inform the CMC, and continue to monitor per applicable Schedule of Evaluations. If after 4 weeks repeat test results of ALT is still ≥ Grade 2, and/or bilirubin is still ≥ Grade 1, continue to hold study product and consult the CMC.</td>
</tr>
<tr>
<td></td>
<td>• If baseline ALT was ≤ ULN and participant is symptomatic (i.e. has nausea, abdominal discomfort or anorexia), regardless of accompanying bilirubin test results: Hold study product, and repeat testing weekly. If repeat test results of ALT return to baseline, resume study product use, inform the CMC, and continue to monitor per applicable Schedule of Evaluations. If after 4 weeks repeat test results are still Grade 2 ALT, continue to hold study product and consult the CMC.</td>
</tr>
<tr>
<td>ALT SEVERITY GRADE WITH ACCOMPANYING BILIRUBIN SEVERITY GRADE (TOTAL OR DIRECT)</td>
<td>PARTICIPANT AND STUDY PRODUCT MANAGEMENT</td>
</tr>
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<tr>
<td>Grade 3 ALT, regardless of accompanying bilirubin test result</td>
<td>Hold study product, inform the CMC within 24 hours, and repeat testing within 72 hours. Reinforce participant awareness and knowledge about signs and symptoms of hepatotoxicity. Participants should be advised to notify the study site immediately if they develop any concerning signs or symptoms: new or worsening nausea, vomiting, unexplained loss of appetite; yellowing of the skin or eyes; increased weakness or fatigue; pain in the upper abdomen (liver tenderness or hepatomegaly); pale or clay-colored stools; and/or unexplained weight loss. Participants should be advised to seek immediate medical attention and contact the site as soon as possible.</td>
</tr>
<tr>
<td>• If repeat test results in ≤ Grade 2 without addressing possible alternative etiology, manage as per Grade 2 above.  • If upon addressing possible alternative etiology repeat test results in ≤ Grade 2, consult CMC. If CMC agrees, resume study product. If event recurs at ≥ Grade 3, permanently discontinue study product and inform CMC.  • If repeat test results in ≥ Grade 3, continue to hold study product and consult the CMC. If no possible alternative cause identified, permanently discontinue study product.</td>
<td></td>
</tr>
<tr>
<td><strong>ALT SEVERITY GRADE WITH ACCOMPANYING BILIRUBIN SEVERITY GRADE (TOTAL OR DIRECT)</strong></td>
<td><strong>PARTICIPANT AND STUDY PRODUCT MANAGEMENT</strong></td>
</tr>
<tr>
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<tr>
<td>Grade 4 ALT, regardless of accompanying bilirubin test result</td>
<td>Hold study product, inform the CMC within 24 hours, and repeat testing within 72 hours. Reinforce participant awareness and knowledge about signs and symptoms of hepatotoxicity. Participants should be advised to notify the study site immediately if they develop any concerning signs or symptoms: new or worsening nausea, vomiting, unexplained loss of appetite; yellowing of the skin or eyes; increased weakness or fatigue; pain in the upper abdomen (liver tenderness or hepatomegaly); pale or clay-colored stools; and/or unexplained weight loss. Participants should be advised to seek immediate medical attention and contact the site as soon as possible.</td>
</tr>
<tr>
<td></td>
<td>• If repeat test results in ≤ Grade 2, manage as per Grade 2 above.</td>
</tr>
<tr>
<td></td>
<td>• If repeat test results in Grade 3, manage as per Grade 3 above.</td>
</tr>
<tr>
<td></td>
<td>• If repeat test result is still Grade 4, inform CMC and permanently discontinue study product.</td>
</tr>
</tbody>
</table>

### 8.1.6 Hypersensitivity Reaction

Hypersensitivity includes a constellation of symptoms such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.

If the IoR or designee suspects hypersensitivity reaction, regardless of relationship to study product, the participant should be managed as follows:

- **Grade 1 or higher**: temporarily hold study product, and within 24 hours of site awareness repeat hematology and chemistries testing on newly obtained samples, and notify the CMC. Continue to re-evaluate the participant, and repeat testing on newly obtained samples at least twice weekly until the abnormal laboratory test results return to baseline values, or stabilize. Refer participant to a specialist or hepatology consultation, at the discretion of the site investigator, and in consultation with the CMC.

### 8.1.7 Allergic Reaction

Participants with allergic reactions should be managed as follows:

- **Grade 1 or higher assessed as not related, and Grades 1 or 2 assessed as related**: continue study product, and antihistamines, topical corticosteroids, or antipruritic agents may be prescribed at the discretion of the IoR or designee. The participant should be
advised to contact the site immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop.

- **Grade 3 or higher assessed as related:** permanently discontinue study product, and notify the CMC within 24 hours. Manage as clinically appropriate including antihistamines, topical corticosteroids, or antipruritic agents. Admission to hospital may be required for severe allergic reactions. Following clinical stabilization, re-evaluate the participant weekly, and manage according to standard of care practice at the site until resolution to baseline.

### 8.1.8 Skin rash

All participants experiencing a rash should be assessed for systemic symptoms, laboratory abnormalities, or mucosal involvement.

Participants with skin rash should be managed as follows, regardless of relationship to study product:

- **Grade 1 (regardless of systemic involvement), or Grade 2 without evidence of systemic involvement:** continue study product use at the discretion of the site investigator.

- **Grade 2 with evidence of systemic involvement, or Grade 3 or higher (regardless of systemic involvement):** permanently discontinue study product, and consult the CMC within 48 hours. Re-evaluate daily for at least 5 days for systemic symptoms, laboratory abnormalities, mucosal involvement, and for any progression of the rash or increase in severity. Cohort 1 participants should also discontinue their cART regimen, at the discretion of the site investigator and in consultation of the CMC. Participants may be referred to a dermatologist, at the discretion of the site investigator.

Additionally, for any rash determined to be related to study product and presenting prior to the Week 4b visit (for both Cohort 1 and Cohort 2 participants), the CMC must be consulted prior to administering injectable study product at the Week 4b visit.

### 8.1.9 Depression, Suicidal Ideation or Attempt

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidal ideation or behavior. Participants who experience symptoms of depression and/or suicidal ideation or behavior, or report delusions and inappropriate behavior, regardless of relationship to study product, should be managed and re-evaluated according to standard of care practice at the site, or more frequently, or referred for specialist evaluation and treatment, at the discretion of the site investigator. Refer to the IMPAACT 2017 MOP for additional guidance regarding establishing a baseline screening assessment for depression. Participants reporting new symptoms of depression will be asked to contact the study IoR or designee immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop. All sites should have a plan in place for managing possible risks for suicide related events.

- **Grades 1 or 2:** manage per site standard of care and SOPs.
- **Grade 3 or higher:** manage per site standard of care and SOPs, and consult the CMC within 24 hours
8.2 Monitoring and Management of QTc Prolongation

Monitoring

An ECG machine that automatically calculates the heart rate and measures QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. The IoR or designee can review the ECG reading and a cardiologist reading is not required. Otherwise, an appropriately qualified ECG reader must interpret the results. At the Screening visit, three single automated QTc readings will be done separated by at least 2 minutes, with the mean value of these readings being used to establish baseline. During follow-up, single automated readings will be compared to the baseline value, with a result of > 500 msec or > 60 msec increase from baseline averaged value requiring a repeat reading in triplicate and averaged QTc calculation (as performed at the Screening visit).

The same QT correction formula (for e.g. Bazett’s or Fridericia's) must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. For example, if a participant is eligible for the protocol based on QTcB (calculated using Bazett’s formula), then QTcB must be used for discontinuation of this individual participant as well. Once the QT correction formula has been chosen for a participant’s eligibility, the same formula must continue to be used for that participant for all QTc data being collected for data analysis.

Management of QTc Prolongation

During follow-up, if a single automated reading results in a QTc interval > 500 msec, or a >60 msec increase from baseline averaged value, repeat the reading in triplicate (i.e. three tracings separated by at least 2 minutes).

- If any one of the repeated readings confirm a QTc interval > 500 msec, or a > 60 msec increase from baseline, temporarily hold study product and assess participant for concomitant medications known to cause prolonged QT or Torsades de pointes.
- Study product may be resumed in consultation with the CMC, and if the prolonged QTc is assessed as not related to study product.
- If the prolonged QTc is assessed as related, or no other likely cause identified, permanently discontinue study product.

For any other abnormal or irregularity reported by the automated read or by the qualified site clinician, a cardiologist should be consulted, and the CMC notified.

8.3 Management of Contraception and Pregnancy

Any female participant of childbearing potential must agree to maintain use of an allowable effective contraceptive method throughout study participation, in addition to:

- at least 30 days after discontinuation of oral study products (if terminating early from the study during Cohort 1 Step 1 or Cohort 2 Step 3), and
- at least 48 weeks after discontinuation of injectable study products.

Counseling should begin during the screening visit and continue for each participant throughout their participation in the study. See Section 6.13 for more details on pregnancy testing, contraceptive counseling, and a list of the allowable effective contraception methods.
For all female participants, a negative pregnancy test result must be obtained on the same day and prior to administration of study product. For females of childbearing potential, confirmation of contraceptive use (per participant report) must also be obtained on the same day and prior to administration of study product. If effective contraception cannot be confirmed, and in the opinion of the investigator early pregnancy cannot be excluded, then study product should be temporarily held and the CMC consulted for further guidance on study product use and participant management.

Female participants with a positive pregnancy test result will temporarily discontinue study product, with confirmatory testing conducted within 48 hours. Upon a confirmatory positive pregnancy test result, study product will be permanently discontinued. Cohort 2 female participants will resume an oral cART regimen. The choice of cART regimen is at the site investigator’s discretion and in accordance with the local standard of care and available resistance profiles, and appropriate for use in pregnancy. Sites should actively refer pregnant participants to antenatal standard of care, and to engage in antenatal care as early in the pregnancy as possible. Additionally, the CMC should be notified within 2 weeks of obtaining the initial positive pregnancy test result.

Pregnant participants in Steps 1 through 4 will be followed per the LSFU visit schedule based on the date of the positive confirmatory test result. Pregnant participants already being followed per the LSFU visit schedule will continue their scheduled visits, however any pregnancy outcome occurring after study exit will be entered into eCRFs, as further described below.

Pregnancy test results and pregnancy outcomes will be ascertained and entered into eCRFs. Pregnancy outcomes should be ascertained based on medical records; when medical records are unavailable, maternal report may be used. For participants who are pregnant at the time of study exit, or early study termination, additional post-study contacts should be completed to ascertain their pregnancy outcomes (see Section 6.8). If the site becomes aware of a pregnancy complication occurring after the participant has exited the study, and the pregnancy complication is assessed as related to study product, the CMC should be notified within 2 weeks of site awareness.

Study sites will also be encouraged to prospectively register the participant’s pregnancy in the Antiretroviral Pregnancy Registry: http://www.apregistry.com/ (in U.S.: 1-800-258-4263).

### 8.4 Monitoring and Management of HIV Viral Load

**Monitoring**

HIV-1 RNA (viral load) will be monitored closely with frequent testing as specified in the Schedules of Evaluations in Appendix I. All HIV-1 RNA assays must be performed in a CLIA-certified (US sites) laboratory using the testing platform specified in the LPC.

Site investigators should review the results of each test as well as trends over time and consult with the CMC regarding any individual test results or trends of concern. As noted in Section 6.5, viral load results should be provided to participants and may be used to guide adherence counseling.

**Definition and Confirmation of Virologic Failure**

Virologic failure is defined as two successive plasma HIV-1 RNA test results ≥200 copies/mL.
Any participant with a plasma HIV-1 RNA level $\geq$200 copies/mL after enrollment should be recallled to the clinic for confirmatory testing 2-4 weeks after specimen collection for the initial test. Specimen collection for antiretroviral resistance testing and other procedures will also be performed at the time of specimen collection for confirmatory HIV-1 RNA testing. Refer to Section 6.6 for more details regarding the visit procedure and scheduling of the Confirmation of Virologic Failure visit.

**Management of Confirmed Virologic Failure**

The CMC should be consulted regarding any participant with confirmed virologic failure. All participants with confirmed virologic failure will be permanently discontinued from study product. Refer to Section 8.7 for participant management regarding permanent discontinuation of study product, and Section 6.5 for those participants who will be followed per the LSFU visit schedule upon permanent discontinuation of study product.

HIV genotypic and phenotypic resistance test results collected at the Confirmation of Virologic Failure visit will be processed and shipped per Section 6.16.2. Resistance testing will be performed in real time, per Section 6.16.2 and the LPC. These resistance test results will be reviewed by the site investigator of record, or designee, and used to inform a recommended cART regimen, in consultation with the CMC. Cohort 1 participants may be recommended to change their ongoing cART regimen, based on these results. Cohort 2 participants should resume the recommended non-study provided oral cART as soon as possible and within 4 weeks.

### 8.5 Substitution or Dose Modification of cART for Cohort 1 Participants

Cohort 1 participants will continue their pre-study cART regimen while receiving study products in both Step 1 and Step 2. Dose changes for growth are permitted. In the event that a change or substitution is required for an acute safety event that requires regimen changes (eg. renal compromise on TDF for which alternative NRTI is sought), sites should consult CMC for guidance for drugs that can be co-administered. Cohort 1 participants will be permanently discontinued from study product use if a cART regimen change is required that would affect Cohort 1C vs Cohort 1R assignment.

### 8.6 Deferring Study Product and Criteria for Temporary Hold of Study Product

At each study product administration time point, the site investigator or designee must confirm participant eligibility to receive study product based on review of medical and medications history, physical examination findings, and prior laboratory test results (see Section 6.9). Study product administration must be deferred consistent with the guidance provided in Section 8.

For any other significant medical condition that, in the opinion of the investigator, would make it unsafe to administer study product or make it difficult to assess for subsequent product related adverse events, if present on the scheduled day of study product administration, administration must be deferred, and the CMC should be consulted on next steps and continued study product management.

For Cohort 2 participants who have a temporary hold, both study products should be held and the CMC should be consulted as soon as possible and within 48 hours of site awareness; the CMC may recommend resuming a (non-study provided) cART regimen in these situations. For participants resuming a cART regimen for the duration of a temporary study product hold, site
staff should provide the participant and the participant’s parent or guardian with referrals to non-
study sources of treatment for the participant, as applicable. See the IMPAACT 2017 MOP for
operational consideration and guidance.

Study product will be temporarily held from a participant for any of the following reasons:

- Study product management per Sections 8.1 through 8.5.

- Report of use of prohibited concomitant medications (as listed in Section 5.7). Study product
use may resume upon consultation with the CMC and when the participant reports that he/she
is no longer taking the prohibited medication, provided other reasons for temporary study
product hold/permanent discontinuation do not apply. The CMC should be consulted in all
cases of a participant reporting taking a prohibited concomitant medication during the course
of the study.

- The participant is unable or unwilling to comply with required study procedures, such as
protocol-required laboratory assessments or injectable study product visits, or otherwise
might be put at undue risk to their safety and well-being by continuing study product use,
according to the judgment of the site investigator. The site investigator must consult the CMC
on all temporary study product holds instituted for this reason, for further guidance on
resuming study product use, continuing the temporary hold, or progressing to permanent
discontinuation.

Participants who temporarily or permanently discontinue oral study product during the oral phase
(Step 1 or Step 3), or during oral bridging (in Step 4) will be instructed to return all oral study
products to the site clinic as soon as possible.

8.7 Criteria for Premature Permanent Discontinuation of Study Product

See Section 8.8 for guidance regarding participant management in the event of early termination
or withdrawal from study participation. Administration of study product will be permanently
discontinued in the following circumstances:

- Participant intention to discontinue study product or study follow-up
- During the oral phase (Cohort 1 Step 1, or Cohort 2 Step 3), sustained non-adherence to oral
regimen (study product, or non-study provided cART for Cohort 1 participants) that, in the
opinion of the investigator and in consultation with the CMC, warrants early study product
discontinuation.
- Sustained non-adherence to injection visit schedule that, in the opinion of the investigator and
in consultation with the CMC, warrants early study product discontinuation (per IoR
discretion, a temporary product hold may be initially implemented; see Section 8.6).
- The participant requires treatment with prohibited medications (see Section 5.7).
- Pregnancy (see Section 8.3)
- The participant experiences an adverse event that requires discontinuation as defined in
Sections 8.1 through 8.5.
- Virologic failure as described in Section 8.4.
- The site investigator determines that further administration of study product would be
detrimental to the participant’s health or well-being.
- New data become available that indicate study products should be discontinued as determined
by the CMC.
In the event of premature permanent discontinuation of study product, participants will either be followed per the LSFU visit schedule or complete an Early Termination visit, as described below. For Cohort 2 participants, in the event of a permanent discontinuation of study product, both study products will always be discontinued, and participants should immediately resume (non-study provided) oral cART.

Upon permanent discontinuation of study product, the following participants will be followed per the LSFU visit schedule:

- Cohort 1 Step 2 participants: prior to receiving the Week 12 study product injection, or completing the Cohort 1 Step 2 Week 16 visit
- Cohort 1 Step 2 participants who enroll to Cohort 2 Step 3 but are not eligible to progress to Cohort 2 Step 4
- Cohort 2 Step 4 participants, including those completing the Cohort 2 Step 4 Week 96 study visit but choosing to not continue to receive injectable CAB LA + RPV LA external to the protocol

Cohort 1 Step 1 and Cohort 2 Step 3 participants (without prior Cohort 1 Step 2 participation) not eligible to progress to their respective injection phase will complete an Early Termination visit upon permanent discontinuation of study product.

8.8 Participant Withdrawal or Termination from the Study

Regardless of the participant retention procedures referenced in Section 4, participants may voluntarily withdraw from the study. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Participant re-locates away from the study site, is otherwise determined to be lost-to-follow-up, or withdraws consent/assent
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, after consultation with the CMC
- The study is stopped or canceled at the discretion of the FDA, IMPAACT, the site IRB or EC, OHRP, NIAID, NICHD, or other country-specific governmental agencies

A participant may voluntarily discontinue study participation at any time, and the site investigator may also, at their discretion, discontinue the participant from the study at any time. Participants who are withdrawn from the study will not be replaced.

Should the consenting parent or guardian of an enrolled participant die or no longer be available for any reason, study product should be temporarily held and no further study products should be administered, cART resumed for Cohort 2 participants, and no further study-specific evaluations should be performed until informed consent for continued study participation is obtained from an authorized guardian, as defined locally. Study sites may continue to provide care for the participant as needed and as appropriate (outside of the study), consistent with the local standard of care, but no study-specific procedures may be performed. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued study participation, the participant must be terminated from the study. Refer to Section 8.6 for additional guidance on communication with the CMC for temporary study product holds, and Section 14.3 for guardian consent for study participation.
For any participant who withdraws/is withdrawn or is terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort complete final evaluations as described in Section 6.5.5. In the event that the circumstances that led to a participant’s withdrawal or termination change (e.g., he or she returns to the study site area after having re-located previously), the site investigator or designee should contact the CMC to discuss options for resumption of follow-up.

9 STATISTICAL CONSIDERATIONS

For all PK-related matters, including PK endpoints, outcome measures and analyses, refer to Section 10.

9.1 General Design Issues

This 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.

This statistical section describes the methodology and analyses planned for the primary endpoints and outcome measures with respect to safety and the secondary endpoints and outcome measures other than PK. Please refer to Section 10 for all matters which deal with pharmacokinetics (PK), including the outcome measures and primary analyses, in more detail.

It is expected that approximately 55 participants will need to be enrolled into Cohort 1 to achieve 35 evaluable participants (20 evaluable for CAB and 15 evaluable for RPV), with CAB and RPV to be evaluated separately in this stage of the study. Most (or all) of these participants are expected to proceed to Cohort 2, where they will take the full regimen (CAB + RPV), consisting of both products. There is not a restriction (minimum or maximum) on the number of eligible Cohort 1 participants allowed to proceed to Cohort 2, to provide the most flexibility in study design. However, the participants who proceed from Cohort 1 to Cohort 2 will be a potentially biased sample, since those who have failed in Cohort 1 will not move into Cohort 2. Moreover, those who do participate in Cohort 1 before joining Cohort 2 will have an atypical history of study product exposure, having taken one of the two products before being exposed to both simultaneously. Thus, it is expected that 100 additional participants will need to be enrolled directly into Cohort 2 to achieve an approximate additional 70 evaluable participants receiving the final recommended dose of CAB and RPV. This sample of participants (approximately 100 for 70 evaluable) will be treated as the primary subgroup of Cohort 2 participants, since their results will be unbiased and will generalize to the population of patients who would be treated by simultaneous exposure to the two study products without a prior period of exposure to one or the other. For regulatory submission purposes, the study needs to accrue a sample of at least 100 participants who have taken the full regimen (CAB and RPV) at the final recommended dose. This requirement will be met with approximately 100 participants directly enrolling into Cohort 2, and any eligible Cohort 1 participants proceeding to Cohort 2.

For the Week 16 (for Cohort 1) or Week 24 (for Cohort 2) analyses, evaluable participants will be defined as (1) having been treated exclusively on the dose determined to be optimal for a given cohort and having either completed all required dosing or exposure to the study products, for both oral and injectable CAB and/or RPV, through Week 16 (Cohort 1) or through Week 24 (Cohort 2), or (2) having been classified as a virologic failure or as a safety failure in the oral or IM
phase, due to a study product-related adverse event occurring during these weeks of treatment. PK evaluability is defined in Section 10 (Clinical Pharmacology Plan section).

There will be two groups in Cohort 1:
- Cohort 1C will take the oral CAB once daily for at least four weeks, in addition to their combination ART (cART) in Step 1, followed by single intramuscular injections of CAB LA every four weeks over an eight-week period in addition to cART in Step 2;
- Cohort 1R will take the oral RPV once daily orally for at least four weeks in addition to cART in Step 1, followed by single intramuscular injections of RPV LA once every four weeks over an eight-week period in addition to cART in Step 2.

Cohort 2 will take CAB + RPV once daily orally for at least four weeks, and up to 6 weeks, (Step 3 oral phase), followed by intramuscular injections of CAB LA + RPV LA once every four weeks for 92 weeks (Step 4 injection phase).

In making dosing decisions, the protocol team will review all safety data, as well as the results of PK data (modeling data as needed). Please refer to Section 9.5.1 (Dose Finding) for the dose-finding algorithm and the safety guidelines for making dosing decisions.

Please see Section 3 (Study Design) and Section 1 for management of participants and criteria for evaluation of Cohort 1 and for opening Cohort 2.

To assess the acceptability and tolerability of the study products based on the perceptions of parents and caregivers, up to 60 parents or caregivers of the adolescent participants, as selected by the protocol team, will be accrued to complete a single qualitative phone interview.

9.2 Outcome Measures

For all PK-related matters, including PK outcome measures and analyses, refer to Section 10.

For safety monitoring and reporting purposes, a study product related AE is defined as an adverse event that is judged (based on attribution by the site with concurrence from the protocol team) to be related to the study products (CAB/RPV).

Primary and secondary outcome measures listed below will be addressed in the study’s primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov. Outcomes of interest intended for subsequent publications are listed under “Other Outcome Measures”.
### 9.2.1 Primary Endpoints and Outcome Measures

#### 9.2.1.1 Safety through Week 4 for oral CAB, through Week 16 (CAB LA or RPV LA) for Cohort 1
- **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

#### 9.2.1.2 Safety through Week 24 for CAB LA+RPV LA for Cohort 2
- **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

### 9.2.2 Secondary Endpoints and Outcome Measures

#### 9.2.2.1 Tolerability of CAB LA or RPV LA through Week 16 for Cohort 1
- 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

#### 9.2.2.2 Acceptability of CAB LA or RPV LA through Week 16 for Cohort 1
- 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

#### 9.2.2.2 Safety through Week 48 for CAB LA+RPV LA for Cohort 2
- **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

#### 9.2.2.3 Virologic activity of CAB LA+RPV LA through Weeks 24 and 48 for Cohort 2
- **Outcome – Plasma HIV-1 RNA**
- **Number of participants with HIV-1 RNA >200 copies/mL, missing HIV-1 RNA, study treatment discontinuations**
### 9.2.3 Other Endpoints and Outcome Measures

#### 9.2.3.1 Tolerability of CAB LA+RPV LA through Week 24, through Week 48, and through Week 96 for Cohort 2
- 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.

#### 9.2.3.2 Acceptability of CAB LA+ RPV LA through Week 24, through Week 48, and through Week 96 for Cohort 2
- 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.

#### 9.2.3.2 Safety through Week 96 weeks for CAB LA+ RPV LA for Cohort 2
- 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

#### 9.2.3.3 Virologic activity of CAB LA+RPV LA through Week 96 for Cohort 2
- Outcome – Plasma HIV-1 RNA
- Number of participants with HIV-1 RNA >200 copies/mL, missing HIV-1 RNA, study treatment discontinuations

#### 9.2.3.4 Immunologic activity of CAB LA+RPV LA through Week 96 for Cohort 2
- CD4 count and percentage

#### 9.2.3.4 Participants’ and parents/caregivers’ overall perceptions of their/their child’s experience with CAB LA and/or RPV LA for Cohorts 1 and 2 as elicited through in-depth interviews centered around an ecological model of health behavior

#### 9.2.3.5 Tolerability through 48 weeks following permanent discontinuation of CAB LA or RPV LA for Cohort 1 and CAB LA+RPV LA for Cohort 2
- 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.

#### 9.2.3.5 Acceptability through 48 weeks following permanent discontinuation of CAB LA or RPV LA for Cohort 1 and CAB LA+RPV LA for Cohort 2
- 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.
9.2.3.6 Long-term safety through 48 weeks following permanent discontinuation of CAB LA or RPV LA for Cohort 1 and CAB LA+RPV LA for Cohort 2
   • Safety Outcome: All adverse events, regardless of grade
   • Number of participants who:
     o Had Grade 3 or higher adverse events
     o Had Grade 3 or higher adverse events assessed as related to study product/s
     o Had serious adverse events meeting ICH criteria assessed as related to study product/s
     o Died due to adverse events assessed as related to study product/s

9.2.3.7 HIV-1 genotype and phenotype resistance to CAB and/or RPV in participants experiencing virologic failure (Cohort 1 and Cohort 2)

9.3 Randomization and Stratification

There will be no randomization for Cohorts 1 and 2. Participants for Cohort 1 will be placed into CAB or RPV arms based on suppressive oral cART at entry: participants on PI-based or NNRTI-based cART will be assigned to Cohort 1C, while participants on INSTI-based cART will be assigned to Cohort 1R. In Cohort 2, participants will all receive both study products.

9.4 Sample Size and Accrual

The sample size is the minimum number of participants, agreed upon by the industry sponsor and regulators and driven primarily by safety considerations, which is likely to be needed to determine the dosage across the possible weight, age and gender distributions. Monte Carlo simulations based on existing PK models in adults with extrapolation to the study population characteristics were performed to estimate the variability for selected primary and secondary parameters and confidence intervals.

(i) To ensure a Cohort 1 sample size able to provide precise estimates of apparent clearance (CL/F) consistent with the FDA guidelines for pediatric trials. Monte Carlo (MC) simulations incorporated adult CAB and RPV population PK model and the expected adolescent IMPAACT 2017 subject characteristics. One hundred virtual PK trials were generated with 20 CAB and 15 RPV simulated subjects for each study. Each simulated trial was analyzed independently for median PK parameter estimates (including CL/F) specific for that trial, resulting in 100 median values for each PK parameter. Confidence intervals of the individual median PK parameters (from each study) were generated from these 100 values. The 90% CI of the medians from the 100 simulated trial CAB CL/F estimates ranged from 0.84 - 1.17 of the overall adolescent median CL/F value and no study estimated deviated from the overall median by > 25%. The corresponding 90% CI for CAB median V/F estimates were 0.92 - 1.09 of the overall median V/F. For RPV the 90% CI for RPV CL/F was 0.86 - 1.15 of the overall adolescent median value.

(ii) To ensure a sample size able to provide precise estimates of oral CAB AUC (Cohort 1C); CAB LA and RPV LA C28D (Cohort 1C and 1R). Simulated PK trials were also used to construct confidence intervals for these exposure parameters. For CAB, the AUC 90% CI ranged from 0.86 - 1.19 of the overall value and the C28D 90% CI ranged from 0.80 - 1.29 of the overall value. For RPV LA the C28D 90% CI ranged from 0.80 - 1.29. While a few individual simulated subjects had concentrations outside of target, all 100 of the virtual trials had median exposure parameters within the target range.
Table 9 presents exact 95% confidence intervals around various potential rates of Grade 3+ AEs which might be observed in a total sample of 100 participants who might contribute data to the safety analysis, a minimum sample of 20 participants from Cohort 1C, a minimum of 15 participants from Cohort 1R, a potential sample of 35 participants which represents the combined arms of Cohort 1, and a potential sample of 70 participants who enrolled directly into Cohort 2 and who will be regarded as the primary sample for the Cohort 2 safety assessment. This table indicates that confidence intervals will be quite wide around the sample size of 15 participants but would be considerably more precise around the target samples of 70 primary or 100 overall Cohort 2 participants.

<table>
<thead>
<tr>
<th>N*</th>
<th>n (%) With ≥ Grade 3 Adverse Events</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0 (0%)</td>
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</tr>
<tr>
<td>20</td>
<td>0 (0%)</td>
<td>0.00, 0.17</td>
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<tr>
<td>35</td>
<td>0 (0%)</td>
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<tr>
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<td>0 (0%)</td>
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<tr>
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<td>0 (0%)</td>
<td>0.00, 0.04</td>
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<tr>
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<td>0.04, 0.48</td>
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<tr>
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<td>0.06, 0.44</td>
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<td>14 (20%)</td>
<td>0.11, 0.31</td>
</tr>
<tr>
<td>100</td>
<td>20 (20%)</td>
<td>0.13, 0.29</td>
</tr>
</tbody>
</table>

* Note: N refers to total sample size of possible sub-group analysis, but note that dosing decisions will make use of all available data.

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard procedures described in the IMPAACT Network Manual of Procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 12 and 13 provide more information concerning on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.5.1 Monitoring by the Protocol Team

9.5.1.1 Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and the quality of study conduct.

The team will closely monitor participant accrual and retention based on reports that will be generated at least monthly by the SDMC. The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. The team will monitor the timing
of site-specific study activation, which will determine when each site will begin accruing participants, and accrual performance following activation. For any site that is delayed in completing the study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers it has encountered and the operational strategies and action plans to address these.

The Protocol Team will monitor participant retention in a manner similar to participant accrual. On behalf of the Protocol Team, the CMC will monitor other key indicators of the quality of study conduct (e.g., adherence to study product regimen, data quality, and data and specimen completeness), based on reports generated by the SDMC, and will take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

9.5.1.2 Participant Safety

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety reports generated by the SDMC. These reports will provide tabulations of adverse events specified for entry into eCRFs, as described in Section 7.2. The CMC will review these reports via conference call or other meeting at least monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs (defined in Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the data reports. The CMC will continually evaluate the pattern and frequency of reported events and will identify any individual issues or trends of concern.

The CMC will also monitor whether any of the safety-related triggers specified in Section 9.5.2 are met. If so, the CMC will rapidly review the triggering events and notify the SMC that an ad hoc review is required. The CMC will likewise request SMC review of any other safety concerns that may be identified throughout the course of the study.

9.5.1.3 Dose Finding

During the dose finding stages of this study (Cohort 1), the CMC will also review the pharmacokinetic data, with the aim of determining the appropriate dose of each product for Cohort 2, while protecting participant safety. The CMC will review PK and safety data reports at least monthly and take action as needed according to the guidelines in Section 10.3 (PK) and Section 9.5.1.2, Participant Safety, above. In addition, the CMC in conjunction with the SMC and the PK committee will discuss any dose adjustment changes based on the PK (of cohort level data) and safety reviews.

Following any pause to address safety concerns, participant accrual may be resumed if resumption is recommended by the CMC and SMC.

Dose Finding Algorithm

Cohort 1

The study will implement a dose-finding algorithm separately for oral CAB/CAB LA and RPV LA based on PK and safety data through Week 16. The PK elements from this algorithm are based on CAB and RPV exposures seen in adult studies that maintain concentrations above the protein adjusted (PA) IC₉₀. Cohorts 1C and 1R will each enroll an initial group of 8 evaluable participants and their PK and safety data will be evaluated as follows:
• If these 8 participants meet the PK guidelines (see Section 10) and there are no safety concerns (see Safety Guidelines for the First 8 Participants Started at a Given Dose Level in Each Group in Cohort 1 below), then the oral/LA IM doses for CAB and LA IM doses for RPV in Cohort 2 will be established and Cohort 2 will begin to accrue, but only with participants who passed Cohort 1, following an SMC review (see Section 9.5.2, Monitoring by the SMC).
• 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 N=8 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 additional 4 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 confirmed by the study team. Additional interim analysis of the PK results may also be performed if any of the study cohorts meets the safety criteria which would trigger an SMC review.
• The doses administered to the group of participants in Cohorts 1C and 1R who meet the PK targets with no safety concerns will be the doses used for Cohort 2.
• Cohort 1 study enrollment and study procedures will not be interrupted for the preliminary PK and safety assessments to be performed on the first 8 participants enrolled into each group.
• Once Cohort 1C and 1R are fully accrued and have data through Week 16, all safety and PK data will be reviewed to confirm that the oral and LA IM doses appear to be safe and to yield therapeutic levels of exposure. Again, if there is uncertainty with respect to the safety data or there is more variability than expected in the PK results in each or both groups of Cohort 1, additional participants may be enrolled.

Cohort 2

Cohort 2 will begin to enroll, starting with the participants who passed Cohort 1, once the dosing of the oral/IM CAB and oral/IM RPV been established, based on data from Cohorts 1C and 1R, as described above. This cohort will be open for accrual to new participants once the full Cohort1C’s N=20 and full Cohort 1R’s N=15 have passed the PK and safety guidelines for Cohort 1 and once the SMC has reviewed available Cohort 1 data and approved enrollment into Cohort 2.

Sparse PK sampling will be collected from Cohort 2 participants to further describe the oral/IM CAB and RPV exposure.

The goal is to enroll 100 evaluable participants in Cohort 2, of which a minimum of 70 will enroll directly into this cohort. Safety and virologic data will be collected longitudinally and analyzed at Weeks 24 and 48.

Safety Guidelines for the Evaluation of Cohort 1 Starting Doses

The study site’s attribution of any serious adverse event to study product will be used for the purposes of employing the start, stop and pause rules. However, when assessments will affect conduct of the study or dose-finding decisions, the CMC will review the AE and the site’s
attribution. In an event of disagreement in assessments, the protocol team will try to reach a consensus with the site with respect to attribution. If this should prove impossible, the SMC will be consulted and will make the final judgment concerning the relationship between study product/s and the adverse event. Gradation of relationship will use the following terminology: ‘Not related’ and “Related”.

Table 10 and Table 11 below use a multinomial response model to assess the probability of failing the safety criteria under each of the hypothetical situations in those tables. The calculations are performed as follows: Each of the total number of subjects represents a trial, which may have 1 of 3 mutually exclusive outcomes: (1) a life threatening study product-related adverse event or a grade 4 event judged to be at least probably related to treatment; (2) a Grade 3+ event, not satisfying the criteria set forth in #1, immediately above, but judged to be at least possibly related to study treatment and resulting in termination of study treatment; and (3) a relatively benign outcome, satisfying neither the criteria in #1 nor #2, immediately above.

Each table has its sets of results under which the set of trials would pass the safety criteria. The probability of passing the safety criteria represents the sum of the probabilities of these sets of results, and “1 minus the probability of passing the safety criteria” represents the probability of failing them. The “True Toxicity Rates” presented in the tables, along with the true rate of having neither of the types of toxicity represented by the true toxicity rates (which is 1 - the sum of the true toxicity rates), provide the probabilities for the outcomes which are used in the multinomial calculations for each of the hypothetical situations.

**Safety Guidelines for the First 8 Evaluable Participants Started at a Given Dose Level in Each Group in Cohort 1**

For each group in Cohort 1, the frequency of adverse reactions to the starting dose of the study medication will be evaluated on the first 8 evaluable participants, and will include all their safety data through the Week 16 visit. Note that all safety data up to the Week 4a visit and any data at the Week 4b visit but prior to administering the injection, will be closely monitored to assess adverse events occurring during the oral dosing. Moreover, safety data will be monitored on frequent conference calls to assess safety across both oral dosing and injections. A CMC review of safety will be required during which accrual into Cohort 1C or 1R will be paused, if the following safety issues are encountered:

If any of the first 8 evaluable participants should experience death or a life-threatening event that is attributable to the study product/s, or 3 or more participants have experienced study product-related Grade 3+ events (excluding injection-site AEs) or have been permanently discontinued from treatment due to study product-related toxicities (regardless of grade), accrual will be stopped into this dose group. In addition, if patterns of concern are noted, a safety review by the CMC will be conducted.

If these safety issues have been encountered, all of the relevant safety and pharmacokinetic data will be reviewed to determine whether it is safe to continue the attempt to find an optimal dose for this group. If the CMC determines that it is safe to proceed, it will recommend any changes in the dosing and/or monitoring procedures which have been judged to be necessary. The SMC will then review all of the relevant safety and pharmacokinetic data, along with the recommendations of the CMC, and will determine whether and under what conditions further dose finding activities for this group may proceed. Note that there may be a point, prior to accruing and evaluating the 8 participants, where it becomes inevitable that the dose under consideration will fail the safety criteria. In this event, the reviews described above will be performed immediately and no further
accrual will occur until the CMC and SMC determine the conditions under which further treatment may proceed.

The protocol will only proceed if this review has led to a CMC recommendation that it is safe to do so and SMC agrees. The safety review may lead to a recommendation that the dose be de-escalated. Before implementing such a recommendation, the CMC will review the PK data to determine whether a lower dose is likely to achieve adequate study product exposure.

If none of the first 8 participants has experienced death or life-threatening event that is attributable to the study products, and fewer than 3 of these 8 participants have experienced study product-related Grade 3+ event (excluding injection-site AEs) or have been permanently discontinued for study product-related toxicities (regardless of grade) then this group has passed the initial safety guidelines. The safety and PK results of the overall group of 20 (Cohort 1C) or 15 (Cohort 1R) participants will be evaluated when all participants in these groups have reached Week 16.

Given the small sample sizes within each cohort, the information available for preliminary safety decisions will be imperfect. Two types of sampling errors are possible:
1) In a group where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines;
2) In a group where the true rate of toxicity is low enough that further exposure to the current starting dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study medication were used extensively among the participant population at the dose level under question. The hypothetical situations presented in Table 10 range from conditions under which a given dose level would cause a high incidence of study product-related severe and life-threatening AEs to conditions under which severe adverse events would be relatively rare and would not be life threatening. For each of these hypothetical situations it is assumed that a sample of 8 participants is drawn from the participant population and that the safety guidelines, summarized above, are followed.

As an example of how to read Table 10, the second row shows that there is a 93% chance of failing the safety guidelines at doses in which the true rate of study product-related life-threatening AEs is 5% and the true rate of study product-related non-life-threatening adverse events is 50%.

### Table 10. Probability of Failing Dose Guidelines Under Potential Rates of True Toxicity

<table>
<thead>
<tr>
<th>True Toxicity Rates</th>
<th>Probability of Failing Safety Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-life threatening study product-related Grade 3+ AEs, Study product related life-threatening Grade 4 AEs</td>
<td>0.86</td>
</tr>
<tr>
<td>0.50 0.00</td>
<td>0.93</td>
</tr>
<tr>
<td>0.50 0.05</td>
<td>1.00</td>
</tr>
<tr>
<td>0.25</td>
<td>0.00</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>0.25</td>
<td>0.05</td>
</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>0.05</td>
<td>0.25</td>
</tr>
<tr>
<td>0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>0.00</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Under the conditions specified in row 2 of the table, assuming that it would be undesirable to treat additional subjects at a dose that had these true rates of adverse events, the 7% chance of NOT failing the safety guidelines would represent the probability of error. As a further example, the table also shows that there is 1% chance of failing, when the true rate of study product-related non-life-threatening AE is only 5% and the true rate of study product-related life-threatening AE is zero. Assuming that the potential benefits associated with exposing additional subjects to this dose of the study product would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

Note that the PK results may indicate that a dosing decision is possible prior to the evaluation of the total sample, but that additional subjects need to be added to the initial samples of 8 participants in order to obtain sufficiently precise estimates of pharmacokinetic parameters. In this case, the safety evaluation criteria will be consistent with those specified above, such that failure would consist of either: 1) a single life threatening toxicity at least possibly attributable to the study drug or 2) more than 25% of the sample having exhibited Grade 3+ toxicities judged to be at least possibly attributable to the study drug.

If the safety criteria discussed above are met by the initial 8 participants treated with each of the study products, and the PK estimates are judged to be sufficiently precise and indicate adequate exposure to each of these medications, then subjects who have participated in Cohort 1 will be allowed to progress to Cohort 2 upon completion of their Week 16 visit.

Moreover, once these safety criteria have been met and full accrual into both Cohort 1 groups is complete, naïve subjects with no Cohort 1 experience will be allowed to enroll directly into Cohort 2. Note that the initial 8 participants in each Cohort 1 group will need PK and safety data through Week 16 before Cohort 2 can open, but additional Cohort 1 participants will not be required to have reached Week 16 before this is allowed.
As some subjects will proceed into Cohort 2 before all Cohort 1 subjects have completed the Week 16 evaluations in that cohort, there is an unlikely but potential risk that the complete Cohort 1 evaluation could possibly lead to different dosing recommendations than those drawn from the preliminary evaluation and used for these initial Cohort 2 enrollees. In that case these enrollees would need to be replaced for the primary assessment of the final Cohort 2 results. Given that this would be undesirable, Cohort 2 will not be allowed to open until Cohort 1 data is sufficiently complete and precise to make it extremely improbable that any remaining data would change the dosing recommendations for Cohort 2. When the protocol team judges this to be the case, it will ask the SMC to review the relevant results before Cohort 2 is allowed to open.

**Safety Guidelines for the Total Group of 20 (Cohort 1-C) or 15 Participants (Cohort 1-R) Started at a Given Dose Level in Cohort 1**

The final safety evaluation of to a given starting dose of the study medication administered to each Cohort 1 group will make use of data from all evaluable participants in that group who started at that dose. The data for the formal safety criteria will extend to the Week 16 visit for participants not requiring PK determined dose adjustment, or until the visit on which the dose is adjusted, should this occur. If any of these participants has experienced death or a life-threatening event that is attributable to the study product/s, or more than 25% of the participants have experienced study product-related Grade 3+ events (excluding injection-site AEs) or have been permanently discontinued from treatment due to study product-related toxicities (regardless of grade), this starting dose will fail the safety guidelines for the group under investigation. If none of these participants has experienced a study product-related death or life-threatening AE and no more than 25% have experienced study product-related Grade 3+events, then this starting dose will pass the safety guidelines for the group under investigation. Some subjects may have Cohort 1 data well beyond Week 16, and the CMC will examine events occurring during this extended time period to determine whether there are serious or life-threatening events which may be study product related and may require SMC review before determining whether and under what conditions further treatment with this dose of the medication may proceed.

As in Table 10, the hypothetical rates of "true toxicity" which could occur if the study medication were used extensively among the participant population at the dose level are again presented in Table 11, this time assuming that a sample of 15 or 20 participants is drawn from the participant population and the safety guidelines allow no drug-related death or life-threatening events or no more than a 25% rate of drug-related Grade 3+ events.

<table>
<thead>
<tr>
<th>True Toxicity Rates</th>
<th>Probability of Failing Safety Guidelines</th>
</tr>
</thead>
</table>
|                      | Cohort 1-C: N=20/  
<p>|                      | Cohort 1-R: N=15                      |
| Non-life threatening study product related Grade 3+ AEs | Study product-related life threatening Grade 4+ AEs | 0.98 / 0.98 |
| 0.50                 | 0.00                                    | 1.00 / 0.99 |
| 0.50                 | 0.05                                    | 1.00 / 1.00 |
| 0.50                 | 0.25                                    | 1.00 / 0.99 |</p>
<table>
<thead>
<tr>
<th>0.25</th>
<th>0.00</th>
<th>0.38 / 0.54</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.05</td>
<td>0.80 / 0.81</td>
</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>1.00 / 1.00</td>
</tr>
<tr>
<td>0.05</td>
<td>0.00</td>
<td>0.00 / 0.01</td>
</tr>
<tr>
<td>0.05</td>
<td>0.05</td>
<td>0.64 / 0.54</td>
</tr>
<tr>
<td>0.05</td>
<td>0.25</td>
<td>1.00 / 0.99</td>
</tr>
<tr>
<td>0.00</td>
<td>0.05</td>
<td>0.64 / 0.54</td>
</tr>
<tr>
<td>0.00</td>
<td>0.25</td>
<td>1.00 / 0.99</td>
</tr>
</tbody>
</table>

Safety Guidelines for the Total Group of Subjects Started at a Given Dose Level in Each Group in Cohort 1 If Additional Participants are Enrolled to Attain More Precise Estimates to Determine Whether PK Targets Have Been Met

It is anticipated that sufficiently precise PK estimates needed to open Cohort 2 to study-naïve will be achieved with sample sizes less than or equal to the total Cohort 1 samples sizes of N=15 and N=20, specified above. However, if it is determined that additional subjects are needed to attain better confidence in achieving the PK targets, the number of participants being evaluated for safety may become higher than N=15 or N=20 presented above. In such cases the formal safety criteria will be as follows: if any of the participants has experienced death or a life-threatening event that is attributable to the study product/s, or more than 25% of the participants have experienced study product-related Grade 3+ event (excluding injection-site AEs) or have been permanently discontinued from treatment due to study product-related toxicities (regardless of grade), the dose under evaluation will fail the safety guidelines. Otherwise, the dose will pass, unless the longer term Cohort 1 data extending beyond the Week 16 visits indicate the need for further CMC/SMC review, in which case that review will determine whether the dose is appropriate.

9.5.2 Monitoring by the SMC

An independent IMPAACT SMC will review this study regularly, following policies described in the IMPAACT Network Manual of Procedures.

SMC reviews will occur at least annually and may also occur on a more frequent or ad hoc basis if any issues or concerns arise, or if requested by the CMC. Reviews will focus on participant accrual, retention, study conduct, and safety. An SMC review of safety and PK data will also take place prior to opening Cohort 2 for accrual. Additional SMC reviews focused on safety may also occur as indicated below (Participant Safety and Dose Determination). Based on any of its
reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges identified during their reviews.

**Study Progress and Quality of Study Conduct**

The SMC will monitor study progress and the quality of study conduct through review of the same types of data reports as the Protocol Team and CMC.

**Participant Safety**

The SMC will monitor participant safety through review of the same types of safety data reports as the CMC, which will be described in a separate Study Monitoring Plan. For ad hoc or triggered safety reviews, more limited data may be provided, focusing on the events that triggered the reviews.

Triggered SMC reviews will occur in the following scenarios:

(1) In the event of any adverse event that is life-threatening or results in death, the CMC will review the event as soon as possible (ideally within three business days of site awareness) and assess its relationship to study product:
   - If either the site investigator or the CMC assesses the event as related to study product/s, participant accrual will immediately be paused. An ad hoc SMC review will be convened as soon as possible to discuss how the study should proceed.
   - If the site investigator and the CMC assess the event as not related to study product, participant accrual will continue. The SMC will be informed of any of these events along with the CMC’s assessment and decision-making.

(2) In the event of any unresolvable disagreement within the CMC on an issue that would impact decision making or if the CMC requests SMC review of any other event or trend of concern, an SMC review of the relevant data will be convened. The CMC may choose to pause participant accrual and/or administration of study product, pending the outcome of the SMC review.

(3) If, for each cohort, more than 25% of the planned total sample for that cohort experiences study product-related Grade 3+ events, an ad hoc SMC review will be convened as soon as possible. The SMC will review all the relevant safety and pharmacokinetic data, along with the recommendations of the CMC, and will determine whether and under what conditions further accrual and/or opening of Cohort 2 may proceed.

**Dose Determination for Cohort 2**

The team and the SMC will review all PK and safety data through Week 16 from initial groups of 8 participants in Cohort 1C and Cohort 1R to determine if Cohort 2 will open to accrual for Cohort 1 participants. If either Cohort 1 group fails the PK targets or there are safety concerns based on safety data through Week 16, an SMC review will be convened to determine under what conditions Cohort 2 may open to Cohort 1 participants.

Another review of available PK and safety data will be performed once the full Cohorts 1C and 1R have been accrued. This review will allow the SMC to determine whether Cohort 2 can be opened for all possible participants.
A final review of safety and PK data will be performed once all Cohort 1 participants have safety PK data through Week 16. This will examine whether the doses determined on the basis of partial data are confirmed on the full dataset. If this review reveals safety concerns or a potential failure to have identified the optimal doses, then the SMC will be consulted.

9.6 Analyses

9.6.1 Analyses of the Dose-Finding Data

The analysis of dose finding data will consist of descriptive statistics summarizing the safety and PK data from the dose finding phase in Cohort 1 of the study. The safety data of all treated participants in Cohort 1 will be used and will be broken down by group (Cohort 1R and Cohort 1C) and will present the results of the safety evaluations applied to each starting dose tested within each group, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each group, every adverse event of grade 3 or higher will be listed, along with patient demographics, the dose prescribed to the participant at the time of the event and the site’s assessment of the probability that this event was due to the study treatment.

9.6.2 Primary Safety Analyses

The primary safety analyses will focus on the Week 4 (CAB), Week 16 (CAB LA or RPV LA) periods for Cohort 1 and Week 24 (oral CAB and oral RPV followed by CAB LA+RPV LA) period for Cohort 2, where the primary analysis will include only participants whose starting dose of the CAB (oral and LA) and/or RPV (oral and LA) has been at the final dose recommended for their cohorts. Note that any subject who started treatment at the final recommended dose, but whose dose was changed due to toxicity would be included in the primary safety analysis and would be classified as a safety failure. An additional requirement for inclusion in the primary analyses for Cohort 2 is that the participants 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.

For each cohort, participants who have been removed from treatment due to toxicities or for being virologic failures or who have had their doses reduced as part of cohort management due to toxicities will be included and treated as safety failures in the primary safety analyses. These primary analyses will be performed after the last participant in the last cohort has completed 24 weeks on therapy, and results will be presented by cohort.

Each participant’s safety data will be summarized as:

1. the worst grade of AEs, and
2. the worst grade of AEs 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 assessed as related to study products,
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 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, broken down by System Organ Class.

In addition, a primary evaluation of safety through Week 16 (Cohort 1) and through Week 24 (Cohort 2) of study treatment will be performed on the data from participants who have been started at the final recommended dose and have remained on that dose for said week periods or have left the study due to safety failure prior to said weeks of exposure (in which case the participant will be analyzed as a failure).

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

Details concerning the analyses will be included in a separate analysis plan.

For regulatory submission purposes, all the above analyses will be performed and will include all Cohort 1 and Cohort 2 evaluable participants. 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.

### 9.6.3 Secondary Analyses

#### 9.6.3.1 Acceptability and Tolerability

Acceptability and tolerability measures on CAB LA or RPV LA reported by the Cohort 1 participants through Week 16 will be summarized.

#### 9.6.3.2 Safety

The Week 16 (for Cohort 1) and 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.

In addition to the primary analyses restricting the sample to appropriate participants as described above, further analyses which include safety data from all treated participants through all mentioned periods will be performed. These secondary safety analyses will cover all safety data collected from first patient exposure to the end of the study. The Cohort 2 secondary analyses will include approximately 35 participants whose treatment started in Cohort 1 at the final recommended dose and who progressed to Cohort 2 after completing participation in Cohort 1 (see Section 9.1 for a discussion of about the potential for selection bias in this group, and this section on how this bias will be addressed).

Descriptive and exposure-related analyses will present safety data from participants whose doses have undergone cohort-based adjustment or 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 of the probability that this event was due to the study products.

9.6.3.3 Virologic activity

Virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed at Weeks 24 and 48 for Cohort 2 participants who have been at the final dose recommended for this cohort. At both of these time points the primary definition of virologic outcome will be calculated according to a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA’s snapshot algorithm. Participants will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest (this window will be defined in the analysis plan) or they have confirmed RNA > 200 copies/mL. In addition, participants will be classified as virologic failures at either of these time points if they prematurely discontinued the study treatment prior to Week 24 or Week 48 time point.

Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the participant is on-treatment within the visit of interest window. The proportions of participants meeting the criteria for virologic success at each of these time points will be bounded by exact 95% confidence intervals, and will be presented both in the aggregate and broken down by cohort.

In addition, the above analyses results will also be presented for all treated Cohort 2 participants.

Table 12 presents exact 95% confidence intervals around various potential rates of virologic success which might be observed in a total sample of 100 participants or in subsamples of various sizes (N=15, 20, 35, 70).

Table 12. Percent of Participants Meeting Criterion for Virologic Success with Exact 95% Confidence Intervals

<table>
<thead>
<tr>
<th>N</th>
<th>% Undetectable RNA</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>20%</td>
<td>0.04, 0.48</td>
</tr>
<tr>
<td>20</td>
<td>20%</td>
<td>0.06, 0.44</td>
</tr>
<tr>
<td>35</td>
<td>20%</td>
<td>0.08, 0.37</td>
</tr>
<tr>
<td>70</td>
<td>20%</td>
<td>0.11, 0.31</td>
</tr>
<tr>
<td>100</td>
<td>20%</td>
<td>0.13, 0.29</td>
</tr>
<tr>
<td>15</td>
<td>40%</td>
<td>0.16, 0.68</td>
</tr>
<tr>
<td>20</td>
<td>40%</td>
<td>0.15, 0.59</td>
</tr>
<tr>
<td>35</td>
<td>40%</td>
<td>0.24, 0.58</td>
</tr>
<tr>
<td>70</td>
<td>40%</td>
<td>0.28, 0.52</td>
</tr>
<tr>
<td>100</td>
<td>40%</td>
<td>0.30, 0.50</td>
</tr>
<tr>
<td>15</td>
<td>80%</td>
<td>0.52, 0.96</td>
</tr>
<tr>
<td>25</td>
<td>80%</td>
<td>0.56, 0.94</td>
</tr>
<tr>
<td>35</td>
<td>80%</td>
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</tr>
<tr>
<td>70</td>
<td>80%</td>
<td>0.69, 0.89</td>
</tr>
<tr>
<td>100</td>
<td>80%</td>
<td>0.71, 0.87</td>
</tr>
</tbody>
</table>
9.6.4 Other Analyses

9.6.4.1 Acceptability and Tolerability

The acceptability and tolerability measures on CAB LA + RPV LA through Week 24, through Week 48, and through Week 96 of Cohort 2 participants who have been at the final dose recommended for this cohort will be summarized. Additionally, these participants’ acceptability and tolerability measures through 48 weeks following permanent discontinuation of CAB LA or RPV LA (Cohort 1), through 48 weeks following permanent discontinuation of CAB LA + RPV LA (Cohort 2) will be summarized. These summaries will also be presented for all treated Cohort 2 participants.

See Section 11.6 for the planned analyses regarding the adolescent and parent/caregiver interviews and relating to the outcomes listed in Section 9.2.3.4 in Section 9.2.

9.6.4.2 Safety

The Week 16 (for Cohort 1) and Week 24 (for Cohort 2) analyses described above for the primary analysis will be repeated as secondary analyses through Week 96 and through 48 weeks following permanent discontinuation of CAB LA or RPV LA, and CAB LA+PRV LA for the same participants mentioned under the primary analysis.

In addition to the primary analyses restricting the sample to appropriate participants as described above, further analyses which include safety data from all treated participants through all mentioned periods will be performed. These secondary safety analyses will cover all safety data collected from first patient exposure to the end of the study. Descriptive and exposure-related analyses will present safety data from participants whose doses have undergone cohort-based adjustment or 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 of the probability that this event was due to the study products.

9.6.4.3 Virologic Activity

The Weeks 24 and 48 analyses described in Section 9.6.2.3 for the secondary analysis on virologic activity will be repeated as other analysis through Week 96 for the same participants mentioned under said secondary analysis. In this analysis, virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed at scheduled time points for Cohort 2 participants. At such time points the primary definition of virologic outcome will be calculated according to a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA’s snapshot algorithm. Subjects will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest (this window will be defined in the analysis plan) or they have confirmed RNA > 200 copies/mL. In addition, subjects will be classified as virologic failures at a particular timepoint if they prematurely discontinued the study treatment prior to that time point under consideration.
9.6.4.4 Immunologic Activity

Absolute values and change from baseline in CD4+ lymphocyte count and percentage will be summarized over time for Cohort 2 participants.

Median and the associated interquartile range for changes in CD4+ count and percentage from baseline to Weeks 24, 48, 72 and 96 will be presented. Missing CD4+ values for participants who discontinued study drug prior to the time point of interest due to safety or virologic failure will be replaced with their baseline CD4+ values.

9.6.4.5 Genotype and Phenotype Resistance

The incidence of HIV drug resistance for Cohorts 1 and 2 participants will be presented descriptively at the point of failure for those who meet the criteria for virologic failure. Participants will be evaluated for HIV genotypic and phenotypic drug resistance CAB and/or RPV.

10 CLINICAL PHARMACOLOGY PLAN

10.1 Clinical Pharmacology Objectives

10.1.1 Cohort 1

Cohort 1C will assess the multiple dose pharmacokinetics of oral CAB 30mg once daily and injectable CAB LA 600mg then 400mg every 4 weeks in HIV-infected virologically suppressed adolescents weighing at least 35kg. Cohort 1R will assess the multiple dose pharmacokinetics of oral RPV 25mg once daily and injectable RPV LA 900mg then 600mg every 4 weeks in a similar population. Since daily oral RPV 25mg is already approved in this population, the approved oral dose will be used for both Cohort 1R and Cohort 2, and only limited intensive RPV PK will be collected in Step 1 (oral lead-in phase) of Cohort 1R. In Cohort 1C and 1R, study product will be added onto the participants’ existing ARV therapy and participants will be assigned into Cohort 1C versus 1R based on the agents used in their suppressive ARV regimen (avoiding study product interactions between the ARVs). Multiple PK samples will be collected throughout the oral and LA dose intervals to allow determination of PK parameters for CAB or RPV, as applicable, using noncompartmental methods. The PK results from Cohorts 1C and 1R will be used to determine oral (CAB only) and LA (CAB and RPV) doses to be used in combination in Cohort 2: oral CAB + oral RPV in Cohort 2, Step 3, and CAB LA+RPV LA in Cohort 2, Step 4. The dosing will be selected based on a comparison with the exposure seen in adults using CAB AUC$_{0-\tau}$ in Step 1 (oral, Cohort 1C only) and the CAB or RPV 28 day concentration sample after the third LA dose (C28D) in Step 2. Based on the known safety profiles for CAB and RPV, there will be more lenience for adolescents to have potentially higher concentrations than adults if higher concentrations are well tolerated and demonstrate an acceptable safety profile.

Primary Objectives with Pharmacology

- 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

Other Objectives with Pharmacology

• To characterize long-term safety and PK through 48 weeks following permanent discontinuation of CAB LA or RPV LA

10.1.2 Cohort 2

Cohort 2 will use CAB and RPV in combination, first oral and then injectable with the LA formulation, as a complete ARV regimen, in HIV-infected virologically suppressed adolescents weighing at least 35kg. The Cohort 2 dosage regimen will be determined in Cohorts 1C and 1R, with the exception of oral RPV which will be dosed at the approved dosage of daily 25 mg. The overall PK goal for Cohort 2 is to confirm that plasma concentrations are similar to those observed in Cohort 1 and there is not significant accumulation with more prolonged LA dosing in Cohort 2. Only sparse PK samples will be collected during Cohort 2 which will limit the PK analysis to descriptive summaries of study product concentrations and future population pharmacokinetic analyses.

Secondary Objectives with Pharmacology

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

Other Objectives with Pharmacology

• To evaluate the safety, antiviral activity, and characterize PK of CAB LA + RPV LA through Week 96 in HIV-infected, virologically suppressed adolescents

• To characterize long-term safety and PK through 48 weeks following permanent discontinuation of CAB LA + RPV LA

10.2 Primary and Secondary Data Cohorts 1 and 2

Demographic data used in the PK analysis will include age, gender, race, ethnicity, height, weight, weight Z score, weight group (35-<50kg vs ≥50kg), BMI, and BSI. Available laboratory data will include SCr, albumin, ALT, bilirubin and hemoglobin. Complete dosing information will also be utilized including dose dates, times, dose amounts, food intake, dose administration location of injections, and sample collection dates and times.

Plasma concentrations will be measured:

• Cohort 1C (CAB)
  o Step 1 (oral dosing): Wk 2: Pre-dose, 1, 2, 3, 4, 8, and 24 h post dose (7 samples)

• Cohort 1R (RPV)
  o Step 1 (oral dosing): Wk 2: Pre-dose, 4, 8, and 24 h post dose (4 samples)

- Cohort 2 (CAB and RPV)
  - Step 3 (oral dosing): Wk 2: Pre-dose and between 2-7h post dose (2 samples)
  - Step 4 (LA dosing): Wk 4b: Pre-dose and 2h post dose, Wk 5: Day 3-7 post-dose, pre-dose prior to every injection at Wk 8, Wk 12, Wk 16, Wk 20, Wk 24, Wk 25 (Day 3-7 post-W24 dose), Wk 36, Wk 48, Wk 60, Wk 72, Wk 84, Wk 96.

- LSFU
  - Samples collected 4, 12, 24, 36 and 48 weeks after the final injection (random PK samples).

Assay Site: Plasma pharmacokinetic samples collected will be sent to the IMPAACT Pharmacology Laboratory listed in the LPC for both CAB and RPV containing specimens. Sample collection, processing, storage and shipping details are provided in the LPC. Of note RPV samples need to be protected from light as detailed in the LPC.

Methods to be used: All assay methods will be standardized with a filed Methods Report, under Good Laboratory Practice (GLP) conditions and cross-validated with primary assay providers used for CAB and RPV. The assays will be performed using HPLC/MS/MS.

Reporting of Assay Data: Cohort 1 samples will be batched and assayed after the first 8 Cohort 1C participants, and again after the first 8 Cohort 1R participants have completed the Wk 16 sample collection. This scheduled interim PK analysis will be used to see if the initial dosing is achieving the PK targets. Assaying of Cohort 2 PK samples through the Wk 24 visit, and then through the Wk 48 visit, will be performed in batches and reported once all participants have completed the Wk 24 and Wk 48 visits, respectively. Remaining Cohort 2 PK samples will be assayed in batches and reported at completion of the study, along with PK samples collected during LSFU for the final PK analyses. PK samples collected from Cohort 2 Wks 60, 72, 84, 96, and collected from any Confirmation of Virologic Failure visit, will be assayed as requested by the team. Additional sample PK analysis may be performed prior to the completion of the study based on the study team’s review of the initial interim analysis or at the request of the CMC or SMC.

10.3 Endpoints and Outcome Measures

<table>
<thead>
<tr>
<th>10.3.1 Primary Endpoints and Outcome Measures</th>
<th>Pharmacokinetic output measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.3.1.1 Pharmacokinetic output measures</td>
<td></td>
</tr>
<tr>
<td>• Cohort 1C – Step 1 PO dosing: Wk 2 AUC, CL/F, Cmax, Tmax, pre-dose concentrations (C₀) and 24hr post concentrations (C₂₄hr).</td>
<td></td>
</tr>
<tr>
<td>• Cohort 1C – Step 2 LA dosing: Wk 16 (28day post dose) concentrations (C₂₈D), Cmax, Tmax Doses 1 and 3, C₀ IM doses 1, 2 and 3, AUC Doses 1 and 3, and accumulation ratio.</td>
<td></td>
</tr>
<tr>
<td>• Cohort 1R – Step 2 LA dosing: Wk 16 (28day post Dose 3) concentrations, Cmax, Tmax Doses 1 and 3, AUC Doses 1 and 3, and accumulation ratio for 28 day post concentrations and AUC (Dose 3:1)</td>
<td></td>
</tr>
</tbody>
</table>
10.3.2 Secondary Endpoints and Outcome Measures

<table>
<thead>
<tr>
<th>10.3.2.1 Pharmacokinetic outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cohort 2: CAB and RPV concentrations following PO administration at Step 3 Wk 2</td>
</tr>
<tr>
<td>• Cohort 2: CAB and RPV concentrations following IM administration at Step 4 from Wk 4b to Wk 24 and accumulation ratio (Wk 24 Dose: Wk 4b Dose)</td>
</tr>
<tr>
<td>• Cohort 2: CAB and RPV concentrations following IM administration at Step 4 from Wk 4b to Wk 48 and accumulation ratio (Wk 48 Pre-dose Conc: Wk 4b Pre-dose concentration)</td>
</tr>
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</table>

10.3.3 Other Endpoints and Outcome Measures

<table>
<thead>
<tr>
<th>10.3.3.1 CAB and RPV Pharmacokinetic outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cohort 2: CAB and RPV concentrations following IM administration at Step 4 from Wk 48 to Wk 96 and accumulation ratio (Wk 96 Pre-dose Concentration: Wk 48 Pre-dose Concentrations).</td>
</tr>
<tr>
<td>• Cohort 1: CAB or RPV concentrations 4 to 48 weeks following final IM dose, percentage of CAB or RPV concentrations above IC₉₀, at each washout visit, terminal slope (λz) and terminal half-life.</td>
</tr>
<tr>
<td>• Cohort 2: CAB and RPV concentrations 4 to 48 weeks following final IM dose, percentage of CAB and RPV concentrations above IC₉₀, at each washout visit, terminal slope (λz) and terminal half-life.</td>
</tr>
</tbody>
</table>

10.4 Study Design, Data Analysis, and Modeling

Pharmacokinetic blood samples will be collected as noted in Section 6.16 and Appendix I-A, Appendix I-B and Appendix I-C. The samples will be 2 mL whole blood for Cohort 1 (and for Cohort 1 participants during the LSFU visit schedule) and 4 mL whole blood for Cohort 2 (and for Cohort 2 participants during the LSFU visit schedule). Cohort 2 plasma samples will be split into individual aliquots for CAB and RPV each containing 0.4-1.2 mL plasma; same will be done for Cohort 2 participants during the LSFU visit schedule. RPV samples should be protected from light at all times from collection through storage. Plasma concentrations will be summarized by Cohort, analyte and nominal time. PK analysis will be performed by noncompartmental methods.

CAB: The observed concentrations and parameter estimates will be compared to those seen in adults (Sections 1.3.6.1 and 1.3.6.2). Specifically, following oral CAB 30mg once daily, concentrations are expected to fall between 3.8 mcg/mL (lower bound of the 95% CI for the geometric mean Cₜ in adults) and 8.9 mcg/mL (the upper bound of the geometric mean Cₘₐₓ in adults) and to be associated with an AUC of 135 mcg*h/mL (average CAB concentrations of 5.6 mcg/mL), similar to the adults value of 134 mcg*h/mL (range 79-208 mcg*h/mL). Following CAB LA, CAB trough concentrations at Wk16 are expected to average between 2.2-2.5 mcg/mL, several fold higher than the PA-IC₉₀ (CAB PA-IC₉₀=0.166 μg/mL). (10)

RPV: The observed concentrations and parameter estimates following IM administration will be compared to those seen in adults (Section 1.3.6.4). Specifically, following RPV LA, the Wk 16 trough RPV concentrations are expected to average between 70-85 ng/mL comparable to adult steady-state troughs of 84.4 + 39%ng/mL and several fold higher than the PA-IC₉₀ (RPV PA-IC₉₀= 12 ng/mL). (14)
A non-compartmental pharmacokinetic analysis will be performed using Certara Phoenix or a similar program on the plasma CAB or RPV concentration-time data generated for each individual in Cohort 1C and 1R. Calculated pharmacokinetic parameters will include as permitted by data: area-under-the-curve during the dosing interval (AUC(0-τ)), maximum concentration (Cmax), time to Cmax (Tmax), apparent clearance (CL/F), terminal rate constant (λz) and the terminal half-life. The accumulation for C28D and AUC from Dose 1 to Dose 3 following LA administration will also be determined. Cmax and Tmax will be taken directly from the observed concentration-time data. Data permitting, the terminal slope, λz, will be determined from log-linear portion of the curve and the half-life (T½) calculated as 0.693/λz. AUC(0-τ) will be determined using the linear trapezoidal method.

10.4.1 Interim Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed as data from each Cohort become available. Data from 8 participants per arm (Cohort 1C and Cohort 1R) through Wk 16 are required prior to opening Cohort 2 to eligible Cohort 1 participants continuing on-study in Cohort 2. Cohort 2 will open to participants who have not participated in Cohort 1 after completion of Cohort 1C and 1R through Wk 16. Dose modifications will be considered at each stage prior to initiating Cohort 2 at discretion of team member review of the PK and safety results. If a dose modification is needed, the new dosage will be studied in Cohort 1 prior to use in Cohort 2.

10.4.2 Population Pharmacokinetic Analysis

Population PK analyses may be performed using the IMPAACT 2017 PK data alone or in combination with existing adult PK data using the computer program NONMEM. There are no population PK analysis outputs required for the dose selection in Cohort 1 nor do any Cohort 1 or 2 PK objectives require population PK analysis for generation. Thus, population PK analysis will be considered outside of the scope of this protocol and will be reported separately. However, other PK analyses of collected data, including population PK evaluations, may be performed to assist the study team with assessment of safety or dosing.

10.5 Expected Outcome

Based on simulations presented in Section 1.3.6, oral and LA regimens in this adolescent patient population are expected to achieve concentrations within an acceptable range of those observed clinically in adults. Trough (Day 28) CAB LA and RPV LA concentrations following IM administration may not have fully achieved steady-drug concentrations after the 3rd dose (Table 4). However, the use of loading doses are expected to bring them within 10-15% and 25-30% percent of steady state for CAB and RPV, respectively. If results deviate from expected predictions, dose modifications will be considered.

PK Acceptance Criteria

Oral CAB (Cohort 1C, Step 1)

The study CAB PK acceptable criteria following oral administration in Cohort 1C Step 1 is a median Wk 2 AUC0–τ between 46 and 277 mcg*h/mL (approximately 33-200% of the geometric mean in adults which is 134 mcg*h/mL). This AUC0–τ is expected to be associated with trough concentrations ≥1.4 mcg/mL or > 8 times the PI-IC90 levels shown to be efficacious in LATTE and LATTE-2. For safety, the maximum observed plasma concentration (Cmax) is predicted not to exceed 15 μg/mL (the upper bound of the 95% confidence interval for Cmax at oral CAB 60mg
once daily in LATTE or 1.6-fold the mean $C_{\text{max}}$ of CAB 30mg). If the oral CAB AUC falls below 46 mcg*h/mL, the study team will review the PK data and consider a dosage increase to oral CAB 60mg once daily. Conversely, if the median AUC$_{0-\tau}$ is > 277 mcg*h/mL, the oral CAB dose may be reduced to 20mg once daily based on the IMPAACT 2017 study team review. The study team will review all of PK parameters following oral CAB, safety and tolerability data to determine if a dose modification is warranted. If a dose increase or decrease is felt to be needed by the IMPAACT 2017 study team, a CAB 10mg tablet will be made available, if required, for oral lead-in. The new dosage will be studied in Cohort 1C before incorporating the dosage into Cohort 2.

The range of acceptable median AUC$_{0-\tau}$ values were selected to achieve minimum exposures to permit careful evaluation of safety and tolerability during oral dosing prior to injectable LA administration. The lower end of this range achieves oral exposures that are still well above daily exposures observed following LA injectable administration and this approach of higher oral exposures relative to LA exposures is consistent with the strategy employed in Phase 3 adult treatment studies. The upper AUC represents an average CAB concentration of 11.5 mcg/mL below the 95% CI for $C_{\text{max}}$ for adults given oral CAB dose 60 mg daily that exhibited favorable safety and tolerability through 96 weeks. Oral CAB AUC criteria are also supported by the CAB QTc study. That study achieved a geometric mean $C_{\text{max}}$ of 22.5 µg/mL without a significant safety signal and is approximately double the upper limit of the target AUC$_{0-\tau}$ associated average concentration. It is also more than double the expected $C_{\text{max}}$ in adolescents, 3-fold above $C_{\text{max}}$ for CAB 30 mg once daily of 7.5 µg/mL (LATTE) and >6-fold above the $C_{\text{max}}$ for CAB LA 400 mg Q4W of 3.5 µg/mL (LATTE-2). This broad range of exposures following oral dosing is acceptable during the short-term 4-6 week oral lead-in period, without need for dose modification, unless failure is demonstrated with respect to safety and/or PK criteria. While AUC$_{0-\tau}$ serves as the primary PK parameter for oral dose determination, the core protocol team in consultation with ViiV Healthcare/GlaxoSmithKline representatives will also consider $C_{\tau}$ and $C_{\text{max}}$ of CAB in their evaluation.

Dose Modification (Cohort 1C, Step 1)

No individual dose modification for the use of short-term oral lead-in will be explored in Cohort 1C. In the event of failure with respect to safety concerns and/or PK criteria that are deemed potentially avoidable by a lower exposure to CAB, as judged by the protocol team, dose adjustment will be considered for a future Cohort 1C, subject to availability of a suitable formulation. Any participant that fails Cohort 1C due to safety concerns will not receive CAB LA in Cohort 1C Step 2.

CAB LA (Cohort 1C, Step 2)

The primary PK parameter for determination of acceptability of the CAB dose following CAB LA administration will be the plasma concentration 28 days following the 3rd injection (Wk 16 C28D trough). The acceptable PK criteria following CAB LA administration in Cohort 1C Step 2 is a median Wk 16 C28D between 0.8 – 6.7 mcg/mL (the range of trough concentrations observed at Wk 24 following 400mg IM Q4W, LATTE-2). The lower limit of 0.8 mcg/mL for the Wk 16 $C_{\tau}$ is approximately 4 times the PA-IC$_{90}$ (0.166 mcg/mL) and based on the variability in C28D LA troughs in adults would maintain levels approximately 4 times the PA-IC90 in the vast majority of participants. For safety, with this range of C28D the $C_{\text{max}}$ is predicted to be well below 15 mcg/mL (the upper bound of the 95% confidence interval for $C_{\text{max}}$ at oral CAB 60mg once daily in LATTE or 1.6-fold the mean $C_{\text{max}}$ of CAB 30mg).
If the median CAB LA C28D is > 6.7 mcg/mL, a reduction of CAB LA dose to 450mg/300mg load/Q4wks will be considered by the IMPAACT 2017 study team. The IMPAACT 2017 study team will review all of the PK, safety and tolerability data to determine if a dose reduction is needed. If the median Wk 16 C28D concentrations is below 0.8 mcg/mL it will likely represent much more rapid adolescent IM absorption than expected. More rapid CAB IM absorption would also be associated with higher peak CAB concentrations than adults. This potential scenario is not amendable to correction with a dosage increase of the CAB LA administration every 4 weeks, as dose increases will lead to even higher CAB Cmax. Therefore, if the median Wk 16 C28D CAB concentration is below 0.8 mcg/mL, the IMPAACT 2017 study team will review the PK data in total to see if there is a viable dosing strategy that can achieve acceptable CAB levels. If a dose modification is felt to be needed by the IMPAACT 2017 study team, the new dosage will be studied in Cohort 1C before incorporating into Cohort 2.

RPV LA (Cohort 1R, Step 2)

The study RPV PK acceptable criteria following LA administration in Cohort 1R Step 2 is a median Cohort 1R Wk 16 C28D (trough) between 39-154 ng/mL (approximately 50-200% of the predicted median in adults of 77.2 ng/mL). The lower limit of 39 ng/mL for the C28D is more than 3 times the PA-IC90. If the median RPV LA C28D is > 154 ng/mL, a reduction of RPV LA dose to 600mg/400mg load/Q4W will be considered by the IMPAACT 2017 study team. The IMPAACT 2017 study team will review all of the PK, safety and tolerability data to determine if a dose reduction is needed.

If the median Wk 16 C28D concentrations is below 39 ng/mL it will likely represent much more rapid adolescent IM absorption than expected. As with CAB, rapid RPV IM absorption would likely be associated with higher peak RPV concentrations than adults and this difference would be exacerbated by a RPV dose increase. Therefore, if the median Wk 16 C28D RPV concentration is below 39 ng/mL, the IMPAACT 2017 study team will review the PK data in total to see if there is a viable dosing strategy that can achieve acceptable RPV levels. If a dose increase or decrease is felt to be needed by the IMPAACT 2017 study team, the new dosage will be studied in Cohort 1R before incorporating into Cohort 2.

11 Qualitative Phone Interviews

A single in-depth qualitative phone interview will be conducted with a sub-set of adolescent participants, as selected by the protocol team, to identify acceptability and tolerability concerns unique to the participant population, and to evaluate adolescent participants’ experience of CAB LA and/or RPV LA. This section provides details on the qualitative phone interviews, including selection of participants, coordinating the phone interviews, conducting the interviews, and data analysis.

See Appendix V-A for details regarding qualitative phone interviews with the parents/caregivers of adolescent participants.

11.1 Sample Size and Selection Process

Adolescent participants will be selected to take part in a single in-depth qualitative interview to achieve up to 30 completed phone interviews in each Cohort (for a maximum of 60 completed phone interviews in Cohort 1 and Cohort 2 combined). The sample size is based on the likely
number of interviews needed to achieve thematic saturation. For each Cohort, selection for the interviews will continue until there is either saturation of themes, or the maximum sample size is reached, whichever occurs first. See Section 11.6 regarding thematic saturation and qualitative interview data analyses.

Self-reported demographics from Screening and Entry visits will be used to inform selection with the goal of balancing participant gender and age (both older and younger adolescents) in the completed interviews. This will ensure that perspectives from both males and females, as well as older and younger participants, are reflected in the final analysis. Additionally, participants who permanently discontinue injectable study product will be purposefully selected to ensure reasons for discontinuing the injections are also reflected in the final analysis. Participants will be selected across multiple sites, but restricted to those willing and able to conduct the interview by phone in English.

Participants will be selected on an on-going basis as they approach the respective interview procedure window for their Cohort, and some participants may be selected after they have entered the interview procedure window. The selection process will continue until thematic saturation or the sample size is reached for each Cohort; see Section 11.2 below for the interview procedure windows for each Cohort. The interviews must be completed within the specified interview window to allow for comparison between participants. Participants enrolling to the study early will thus be selected for interviews first, as they will be the first to enter the specified interview windows.

11.2 Qualitative Phone Interview Procedural Window

The qualitative phone interviews will be conducted with selected participants within the following timeframes:
- For selected Cohort 1 participants: Between the Week 4b and Week 12 visits (inclusive), or during LSFU visits.
- For selected Cohort 2 participants: Between the Week 24 and Week 96 visits (inclusive), or during LSFU visits.

11.3 Consenting Considerations and Scheduling Qualitative Phone Interviews

For all adolescent participants, consent (or assent, as applicable) for the possibility of being selected for a phone interview will be obtained from the adolescent and their parent/guardian as part of the informed consent process (or informed assent process, as applicable) for the IMPAACT 2017 study. The protocol interview team will notify site staff when participants are selected for an interview; see Section 11.1 above for details on the selection process.

Upon notification of selection by the protocol interview team, site staff will approach selected participants (either in person or by phone) to confirm willingness to take part in the phone interview. Willingness to take part in the phone interview does not affect overall study participation or other scheduled study visit procedures.

Upon confirmation of the selected participant being willing to take part in the phone interview, site staff will work with the protocol interview team and the selected participant to schedule the phone interview. Operational considerations and guidance, including coordinating the interview, are provided in the IMPAACT 2017 MOP.
11.4 Conducting Qualitative Phone Interviews

Once the phone interview is scheduled, site staff will provide the selected participant with detailed instructions and guidance on accessing the phone interview platform. Phone interviews may be completed either in the study clinic during a scheduled study visit, or from a phone outside the study clinic at a time that is convenient for the participant and within the interview procedural window. All phone interviews will be conducted by a protocol interview team member external to participating clinical research sites, following an interview guide, and will be audio recorded and transcribed.

Sites must source document notification by the protocol interview team of participant selection, and all attempts to contact the participant. Sites must source document and enter into eCRFs willingness to take part in the phone interview, whether they are able to conduct the interview in English, and the date the phone interview occurred. Operational and logistical details regarding communication with the protocol interview team members and site staff are provided in the IMPAACT 2017 MOP.

11.5 Disclosure of Harm

As described above, the purpose of conducting in-depth qualitative phone interviews with participants is to identify acceptability and tolerability concerns unique to the participant population, and to evaluate adolescent participant’s experience of CAB LA and/or RPV LA. Conducting the interviews is not expected to increase the likelihood or risk of self-harm or harm to others.

During the consent (or assent, as applicable) process, participants will be informed that the information that they provide in the interview will be kept confidential, with the exception of disclosures of significant risk for harm, including being abused or experiencing violence, suicidality or homicidality.

If at any time during a qualitative phone interview, a participant divulges that s/he is at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states s/he is suicidal or homicidal, the following will occur to ensure his or her safety:

- The protocol interview team member conducting the interview will immediately contact the site IoR or designee and share any time-sensitive, potentially life-threatening information received from the study participant as part of the phone interview discussions.
- The IoR or designee contacted with this information will follow local policies for management of such situations including engaging immediate/first responders as applicable.
- The IoR or designee will also follow local reporting policies and legal statutes, including reporting to child protection or other appropriate agencies, as well as arranging referrals to appropriate support, counseling or treatment resources.

After the safety of the participant is addressed according to the steps above, the IoR or designee will notify the CMC and document the event, as applicable per Section 7.
To facilitate rapid communications, the IoR or designee is expected to provide up-to-date contact information to the protocol interview team while phone interviews are being scheduled and conducted with participants from the site.

11.6 Qualitative Phone Interview Data Analyses

This section provides an overview of the qualitative data analysis process, which will be a descriptive analysis without formal inference, with a more detailed description presented in the qualitative analysis plan. See Section 12 for details regarding data management responsibilities and source data of the in-depth qualitative phone interviews, audio files, and transcriptions.

Analysis will begin during data collection to allow for an iterative process through which questions and probes can be refined to enhance the depth of understanding elicited, so that topics for further exploration can be noted and incorporated into ongoing interviews. Contemporaneous analysis will also be used for determination of the achievement of thematic saturation. Thematic saturation is determined on the basis of analysis of the completed scripts by multiple investigators who agree that novel information has ceased to arise as new interviews are completed. The qualitative data analysis will utilize a thematic approach whereby the protocol interview team will search for patterns in data and will conceptualize ideas that help explain the presence of those patterns (18). Analysis of textual data will consist of 5 main steps:

1) Reading for content: Analysis will begin with reading and rereading transcripts until content becomes intimately familiar (19). As data are reviewed, emergent themes will be noted;
2) Coding: A list of codes will be created based on both pre-specified and identified themes. Codes will then be assigned to specific sections of text so that the text can be easily and meaningfully searched (20). Code definitions will be documented in a code book and will include information about the code’s central meaning and may also provide examples of text considered within and outside the code’s parameters (19). To ensure inter-coder reliability, all transcripts will be double-coded (i.e. by two separate coders who will compare and reconcile coding results);
3) Displaying: Once transcripts have been coded, principle sub-themes will be identified within each code that reflect finer distinctions in the data;
4) Data Reduction: Matrices and tables that categorize and display data will be used to help the analysts understand the dimensions by which the data are categorized and facilitate comparisons (20);
5) Interpretation: Themes will be identified and explained. Relationships between themes and speakers (e.g. adolescents/parents, males/females, older/younger adolescents) will be mapped to highlight similarities and differences of perspective.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Management Responsibilities

As described in Section 4.7, data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled adolescent participants, and all enrolled parents/caregivers, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation.
specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 12.2).

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Subject Enrollment System is available on the DMC portal at: https://www.frontierscience.org

The protocol interview team at the Children’s Hospital of Philadelphia (CHOP) will collect and manage qualitative phone interview data for the study. In-depth phone interview guides will be developed by the protocol interview team at CHOP and will receive IRB/EC review and approval. The protocol interview team at CHOP will conduct the phone interviews with participants (and parents/caregivers) using a secure teleconference platform. The phone interviews will be digitally audio recorded, downloaded to a secure server, and subsequently transcribed by an external transcription service. The audio recordings and transcripts will be securely electronically transferred to the protocol interview team at CHOP. Transcripts will then be processed by the protocol interview team at CHOP for quality assurance, including ensuring that all personal identifiers have been removed. After completion of quality assurance processing, de-identified transcripts will be labeled as final source data of the phone interview. The audio recordings and transcripts generated by the external transcription service will be deleted from their secure server, as well as from any back-up servers. The audio recordings and finalized transcripts will be kept on a password-protected secure server at CHOP. At no time will study sites have access to the audio files or the transcripts.

The finalized transcriptions of interviews will be uploaded and managed by the protocol interview team at CHOP using a qualitative software package (e.g. NVivo). The DMC will serve as a repository for the following data, which will be securely transferred by the protocol interview team at CHOP: finalized transcripts, codebook, and output data.

### 12.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at:
https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

In-depth qualitative phone interviews will be digitally audio-recorded and transcribed. See Section 12.1 above regarding data management and processing of the audio files and transcripts.
Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study products for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, ViiV Healthcare, the US Food and Drug Administration, site drug regulatory authorities, site IRBs/ECs, OHRP, and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID.

12.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

13 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records including consent and/or assent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. The monitors will also review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

14 HUMAN SUBJECTS PROTECTIONS

14.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific ICFs in accordance with 45 CRF 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval, and continuing review to
the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 15.2).

14.2 Vulnerable Participants

The NIH is mandated by law to ensure that children be included in clinical research when appropriate (21, 22). This study responds to that mandate and will provide clinical research data to inform oral CAB, CAB LA, RPV LA, as well as oral CAB + oral RPV, and CAB LA + RPV LA safety and dosing in children and adolescents. Nonetheless, the children and adolescents who take part in this study are considered vulnerable participants per the US Code of Federal Regulations, and site IRBs/ECs must consider the potential risks and benefits to child and adolescent participants as described in 45 CFR 46 Subpart D (for children).

With respect to 45 CFR 46 Subpart D, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 15.2, and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

14.3 Informed Consent

This section provides details regarding informed consent and assent requirements and procedures for adolescents. Refer to Section 4.7 and the IMPAACT 2017 MOP for further information on informed consent and assent procedures for this study.

As indicated in Section 4.1.2, site investigators and their designees will be required to determine participant age and ability to provide independent informed consent for study participation consistent with IRB/EC policies and procedures. Each site must establish SOPs, roles, and responsibilities for completing these determinations, and study staff involved in completing these determinations must have documented training in the relevant policies and procedures prior to study initiation.

Written informed consent and written assent will be obtained for study participation as follows:

- **If the potential participant is not of legal age to provide independent informed consent as determined by site SOPs:** Parent, legal guardian, or other legally authorized representative must provide written informed consent for study participation and the potential participant must provide written assent for study participation.
Note: Refer to Section 14.2 for considerations related to parental consenting requirements; IRB/EC risk determinations will guide whether the consent of one or both parents may be required for this study. All IRB/EC requirements must be followed.

- **If the potential participant is of legal age and able to provide independent informed consent as determined by site SOPs:** The potential participant must provide written informed consent for study participation.

Written informed consent and assent (as applicable) for participation will be obtained before any study-specific procedures are performed. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will describe what is known about the safety and tolerability of the study products and participants and parents/guardians will be extensively counseled on the importance of adherence to the study product regimen, as well as to cART regimen (for Cohort 1 and LSFU). The informed assent process will include a similar process, with the amount of information and level of detail provided as part of assent processes tailored to the age of the potential participant, guided by IRB/EC policies and procedures.

As part of the informed consent and assent process, consenters will be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been performed. This storage and future use is optional and may be declined with no impact on other aspects of study participation. Likewise, genetic testing of residual specimens is optional and may be declined.

Appendix II provides sample informed consent forms for obtaining parent or legal guardian consent for study participation for adolescents who are unable to provide consent. Appendix III: provides sample informed consent forms for adolescents who are able to provide consent for their own study participation (i.e., do not require parent or legal guardian consent). Appendix IV provides sample informed assent forms for adolescents who are unable to provide consent (i.e., require parent or legal guardian consent for study participation). Each of these appendices also includes a sample consent or assent form for storage and future research testing (Appendix II-C: , Appendix III-C, and Appendix IV-C). All sample informed consent and assent forms provided in Appendix II-Appendix IV may be modified by sites to meet IRB/EC requirements. Study sites are permitted to develop separate assent and consent forms for this study, if required by site or IRB/EC policies and procedures; for example, sites may develop one assent form for children 6 to 11 years of age at lower reading and comprehension levels than another assent form for children 12 to less than 18 years of age.

If the participant, parent, or guardian (as applicable) is unable to read, the process for consenting illiterate participants, as defined or approved by the local IRB/EC, should be followed. Sites must also establish and maintain written procedures describing standards for obtaining informed assent, reflective of applicable IRB/EC guidance.

As indicated above, parental consenting requirements at each site will depend on the IRB/EC risk determination described in Section 14.2; all IRB/EC requirements will be followed. Participants enrolling in the study as minors will generally require consent from a parent or guardian.

In general, each participant is expected to take part in the informed consent process with his or her parent or legal guardian, and both the assent of the participant and the consent of the parent or legal guardian will be required for all consent decisions. For example, if the participant does not
provide assent, or the parent or legal guardian does not provide consent, the participant will not be enrolled in the study. The same approach will be taken for consent for storage and future research testing of biological specimens. However, should the participant be unaware of his/her HIV infection status, the informed consent process may be conducted with the parent or legal guardian separately and without the presence of the participant, per IRB/EC policies. In these circumstances, the assent process must be conducted with both the parent or legal guardian and the participant present. Per IRB/EC policies, sites may modify the consent and/or assent (as applicable) forms and processes to remove mentioning of HIV for participants who do not know their status.

Should the consenting parent (or guardian) of a participant die or no longer be available for any reason, sites should follow the guidelines and procedures in Section 8.8, in addition to those described by their IRBs/ECs. Study sites may continue to provide care for the participant as needed and appropriate (outside of the study), consistent with local standard of care. If a guardian cannot be identified, or if the guardian does not consent to continued study participation, the participant must be withdrawn from the study. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 14.2), all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled child or adolescent, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

Participants may also reach the legal age of consent during follow-up. In this case, written informed consent for continued participation (Appendix III-A and Appendix III-B) and specimen storage and future use (Appendix III-C) will be obtained from participants once they reach legal age at their next study visit. If participants do not consent for continued study participation, they should be discontinued from the study; similarly, if they do not consent for specimen storage and future use, all specimens will be destroyed after all protocol-related testing is complete.

See Appendix V-A for informed consent considerations for parent/caregivers who may enroll to the study to participate in a single in-depth qualitative phone interview.

14.4 Potential Benefits

There may be no direct benefit to participants who take part in this study although there is a potential benefit for improved understanding of, and engagement in, HIV care. Information learned in this study may be of benefit to participants and others in the future, particularly information that may lead to more treatment options for HIV-infected children and adolescents. As mentioned in Section 1.4 there is also the potential risk-benefit of early access to Cohort 2 and its related benefits with the opportunity to stop oral cART and switch to an entirely long-acting injectable regimen. Lastly, participants may also appreciate the opportunity for themselves to contribute to HIV-related research.

14.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and risks associated with receipt of CAB and RPV.

Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, swelling, or fainting. There is a very
small chance of infection where the needle is inserted, though the injections may cause pain, swelling, reddening of the skin, and nodule formations where the needle is inserted.

Although there is already a great deal of robust safety, PK and efficacy data in adults, these drugs have not yet been studied in adolescents. There may also be additional risks associated with use of these study products in adolescence. Refer to Section 1.2.3 for a complete description of the potential risks associated with the use of these drugs.

Dolutegravir (DTG) taken at the time of conception or very early pregnancy may be associated with neural tube defects (NTD) in the fetus. There is no evidence that the risk of NTDs or other birth defects is increased when DTG is started after the early first trimester of pregnancy. Cabotegravir is not dolutegravir. While these medications share a common molecular backbone, and have a similar mechanism of activity, they are separate chemical compounds and have differences in antiviral activity, pharmacokinetics, metabolism and drug-drug interactions. It is not known if the safety signal identified with dolutegravir will be observed with cabotegravir. Cabotegravir was evaluated in a complete package of reproductive toxicology studies, including embryofetal development studies, and no safety findings suggestive of teratogenesis or neural tube defects were identified in the December 2017 version of the Investigator’s Brochure. Every effort will be made in this study to avoid the occurrence of pregnancies among female participants.

The CAB LA and RPV LA injections are long-acting and may be present in the participant’s blood one year, and in for some participants more than one year, after a single injection. The amount of drug will decrease overtime and will eventually disappear.

For virologically suppressed, ART-experienced participants enrolling into Cohort 2, and dropping their background cART, there is the potential risk that the study products may not be as effective in maintaining viral suppression as participants’ current regimen.

Despite all efforts to maintain confidentiality, involvement in the study could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because participants could become known as having HIV). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities. Refer to Section 14.7 for further information on privacy and confidentiality.

14.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs or other materials if applicable per IRC/EC policies and procedures.

14.7 Privacy and Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission from the parent/guardian, as well as the adolescent, to do so except as necessary for review, monitoring, and/or auditing as described in Section 12.2.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms) will be identified by PID
only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only. Audio files and transcripts will be kept on a secure and password protected server with the protocol interview team, and will be identified by PID only when transmitted to contracting services (e.g., a transcription service provider).

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been obtained for this study from the US Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any US Federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants. Because the certificate cannot be enforced outside of the US, however, it applies only to US sites and participants.

14.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV infection identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

14.9 Management of Incidental Findings

Site clinicians will inform parents (or other authorized guardians if applicable) of all clinically meaningful physical exam findings and laboratory test results, including results of HIV tests (if applicable), and hematology and chemistry tests. Pregnancy test results will be disclosed to participants and their parent/guardians consistent with local standards of care; local standard procedures will be noted in site-specific informed consent and assent forms. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

14.10 Management of New Information Pertinent to Study Participation

Participants, and their parent (or other authorized guardians if applicable) will be provided any new information learned over the course of the study that may affect their willingness to allow their adolescent to continue receiving study product and/or remain in follow-up in the study.

14.11 Post-Trial Access to Study Product

Participants will be transitioned into care and treatment outside of the study at the end of their study participation. If CAB LA + RPV LA is not locally available for a participant in Cohort 2 completing the study, then the pharmaceutical company or their partners will provide access CAB LA + RPV LA following the participant’s completion of the study through a mechanism outside of the IMPAACT 2017 protocol until one or more of the following events occur:

- CAB LA + RPV LA is available from another source (e.g., government programs, aid programs, assistance programs, etc.); OR
- If development of CAB LA + RPV LA is terminated, if this occurs.

15 ADMINISTRATIVE PROCEDURES

15.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). Study products are provided by ViiV Healthcare; however, this organization is not involved in sponsorship or regulatory oversight of this study.

The Division of AIDS (DAIDS) within the NIAID is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 13. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US and local regulatory requirements.

15.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRB/EC, local IBC, and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICFs will NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available on the RSC website: http://rsc.tech-res.com/protocolregistration/
15.3 **Study Implementation**

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US and local regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the IMPAACT web site: www.impaactnetwork.org.

Study implementation at each site will also be guided by site-specific SOPs. The DAIDS policy on Requirements for Manual of Procedures specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 12.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

15.4 **Protocol Deviation Reporting**

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 12.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Network Manual of Procedures.

15.5 **Critical Event Reporting**

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at: https://www.niaid.nih.gov/sites/default/files/criticaleventsmanual.pdf

15.6 **ClinicalTrials.gov**

This protocol is subject to the United States Food and Drug Administration Amendments Act of 2007 (FDAAA), including registration in ClinicalTrials.gov.

16 **PUBLICATIONS**

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Network Manual of Procedures.
REFERENCES

RPV as Two Drug IM Maintenance Therapy: LATTE-2 Week 96 Results. 9th IAS Conference on HIV Science; 2017; Paris, France.


20. Miles MB, Huberman AM. Qualitative data analysis: An expanded sourcebook: sage; 1994.


### Appendix I: Schedule of Evaluations

#### Appendix I-A: Schedule of Evaluations for Cohort 1 Adolescents (Cohort 1C and Cohort 1R)

<table>
<thead>
<tr>
<th>Study Visit¹</th>
<th>CT 1 Screen</th>
<th>Step 1 (oral phase)</th>
<th>Step 2 (injection phase)</th>
<th>Confirmation of Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CT 1 Entry</td>
<td>CT 1 Wk 2</td>
<td>CT 1 Wk 4a</td>
</tr>
</tbody>
</table>

#### Behavioral Evaluations

- Acceptability/Tolerability assessment: X * * X * * X * X X X X X
- Qualitative Interview: * * * * * * *

#### Clinical Evaluations

- Medical history: X X X X X X X X X X X X X
- Adherence assessment: X X X
- Complete physical examination: X X
- Symptom-directed physical examination: X X X X X X * X X X X X
- Sexual Maturity Rating: X
- ECG: * X

#### Study Product

- Dispense oral study product (for up to 6 wks): X * *
- Administer injection study product: X X X

#### Laboratory Evaluations

- hCG (females only): X X X X X X X X X
- Confirmation of HIV infection: 0-6 mL
- Hematology: 2 mL 2 mL 2 mL 2 mL 2 mL 2 mL 2 mL 2 mL 2 mL 2 mL 2 mL
- Chemistries: 3 mL 3 mL 3 mL 3 mL 3 mL 3 mL 3 mL 3 mL 3 mL 3 mL
- CD4 count and percentage: 3 mL
- HIV-1 RNA: 6 mL 6 mL 6 mL 6 mL 6 mL 6 mL 6 mL 6 mL 6 mL 6 mL
- Plasma for genotypic and phenotypic resistance testing: 6 mL 6 mL 6 mL 6 mL 6 mL 6 mL 6 mL 6 mL

#### Pharmacology

- PK Sampling: 8-14 mL 4 mL 2 mL 2 mL 2 mL 4 mL 2 mL 2 mL 2 mL 2 mL
- Total maximum blood volume: 17-23 mL 20 mL 25-31 mL 5 mL 16 mL 7 mL 2 mL 19 mL 21 mL 7 mL 2 mL 21 mL 14 mL
Notes:  X – required; * - if indicated

1) Target dates and visit windows may vary per visit. See Section 6.3 for Cohort 1 study visits, procedures, and target dates associated with each visit. See Section 6.1 for further details regarding target dates, target visit windows, and allowable visit windows. See Section 6.5.5 and Appendix I-C for details on conducting an Early Termination visit.

2) The Cohort 1 Step 2 Week 9 visit may be conducted over the phone or in person. See Section 6.3.8 for more details regarding this visit.

3) Acceptability/tolerability assessment questionnaires will be administered at visits during which permanent study product discontinuation is initiated (as indicated), as well as at required Cohort 1 study visits: Step 1 Entry, Week 4b, Week 8, Week 12, and Week 16. See Section 6.15 and the IMPAACT 2017 MOP for further details on the specific questionnaires and timing of administration.

4) Only a sub-set of participants will conduct the qualitative phone interview. See Section 11 for qualitative interview window and details on participant selection.

5) See Section 6.12 for details regarding performing an ECG/EKG.

6) Plasma collected at the Confirmation of Virologic Failure visit for genotypic and phenotypic resistance testing will be shipped per the LPC for testing. Plasma samples collected at all other visits for genotypic and phenotypic resistance testing will be stored for testing as requested by the team. See Section 6.16 and the LPC for more details.

7) See Sections 6.3 and 6.6 for PK sample collection timepoints and windows.
### Appendix I-B: Schedule of Evaluations for Cohort 2 Adolescents

#### Cohort 2 (CT 2)

<table>
<thead>
<tr>
<th>Study Visit¹</th>
<th>CT 2 Screen</th>
<th>Step 3 (oral phase)</th>
<th>Step 4 (injection phase)</th>
<th>CT 2 Q4 weeks (Wk 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96)</th>
<th>Confirmation of Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT 2 Entry</td>
<td>CT 2 Wk 2</td>
<td>CT 2 Wk 4a</td>
<td>CT 2 Wk 4b</td>
<td>CT 2 Wk 8,12,</td>
</tr>
<tr>
<td><strong>Behavioral Evaluations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptability/ Tolerability assessment²</td>
<td>X</td>
<td>*</td>
<td>*</td>
<td>X</td>
<td>*</td>
</tr>
<tr>
<td>Qualitative Interview³</td>
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<td><strong>Clinical Evaluations</strong></td>
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<td></td>
</tr>
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<td>Medical history</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adherence assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete physical examination</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom-directed physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X (except Wk 24)</td>
</tr>
<tr>
<td>Sexual Maturity Rating</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG⁴</td>
<td>X</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study Product</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense oral study product (for up to 6 wks)</td>
<td>X</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer injection study product</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Evaluations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG (females only)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Confirmation of HIV infection</td>
<td>0-6 mL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
</tbody>
</table>

¹ Study Visit:
- CT 2 Screen: Entry, Wk 2, Wk 4a (Step 4 Entry), Wk 5, Wk 8,12, 16,20,24, Wk 25, Wk 28,32,36,40,44,48, Wk 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96.

² Acceptability/ Tolerability assessment:
- X (Wk 8, 12, and 24) | X (Wk 48) | X (Wk 96)

³ Qualitative Interview:
- Only Wk 24 | * | * | *

⁴ ECG:
- Only Wk 24 | Only Wk 48 | Only Wk 96

⁵ Symptom-directed physical examination:
- X (except Wk 24) | X (except Wk 48) | X (except Wk 96) | X

⁶ Sexual Maturity Rating:
- Only Wk 24 | Only Wk 96

⁷ hCG (females only):
- X | X | X | X | X | X | X | X | X

⁸ Confirmation of HIV infection:
- 0-6 mL* | | | | | | | | |
<table>
<thead>
<tr>
<th>Chemistries</th>
<th>3 mL</th>
<th>3 mL</th>
<th>3 mL</th>
<th>3 mL</th>
<th>3 mL</th>
<th>3 mL</th>
<th>Only Wks 60, 72, 84, 96 (3 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count and percentage</td>
<td></td>
<td>3 mL</td>
<td></td>
<td></td>
<td>Wk 24 only (3 mL)</td>
<td>Wk 48 only (3 mL)</td>
<td>Only Wks 72 and 96 (3 mL)</td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>Only Wks 60, 72, 84, 96 (6 mL)</td>
</tr>
<tr>
<td>Plasma for genotypic</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>Only Wks 60, 72, 84, 96 (6 mL)</td>
</tr>
<tr>
<td>and phenotypic resistance testing⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Sampling³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total maximum blood volume</td>
<td>17-23 mL</td>
<td>20 mL</td>
<td>25 mL</td>
<td>5 mL</td>
<td>20 mL</td>
<td>9 mL</td>
<td>24 mL</td>
</tr>
</tbody>
</table>

Notes:  
X – required; * - if indicated

1) Target dates and visit windows may vary per visit. See Section 6.4 for Cohort 2 study visits, procedures, and target dates associated with each visit. See Section 6.1 for further details regarding target dates, target visit windows, and allowable visit windows. See Section 6.5.5 and Appendix I-C for details on conducting an Early Termination visit.

2) Acceptability/tolerability assessment questionnaires will be administered at visits during which permanent study product discontinuation is initiated (as indicated), as well as at required Cohort 2 study visits: Step 3 Entry, Week 4b, 8, 12, 24, 48, and Week 96. See Section 6.15 and the IMPAACT 2017 MOP for further details on the specific questionnaires and timing of administration.

3) Only a sub-set of participants will conduct the qualitative phone interview. See Section 11 for qualitative interview window and details on participant selection.

4) See Section 6.12 for details regarding performing an ECG/EKG.

5) Plasma collected at the Confirmation of Virologic Failure visit for genotypic and phenotypic resistance testing will be shipped per the LPC for testing. Plasma samples collected at all other visits for genotypic and phenotypic resistance testing will be stored for testing as requested by the team. See Section 6.16 and the LPC for more details.

6) See Sections 6.4 and 6.6 for PK sample collection timepoints and windows.
## Appendix I-C: Schedule of Evaluations for Long-Term Safety and Washout PK Follow-Up (LSFU) Adolescents
(Cohort 1 Step 2 and Cohort 2 Step 4 participants who have been permanently discontinued from injectable study product, and pregnant participants)

<table>
<thead>
<tr>
<th>Study Visit¹</th>
<th>LSFU Week 4²</th>
<th>LSFU Week 12</th>
<th>LSFU Week 24</th>
<th>LSFU Week 36</th>
<th>LSFU Week 48/Early Termination³</th>
<th>Confirmation of Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral Evaluations</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Acceptability/Tolerability assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Qualitative Interview⁴</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>Clinical Evaluations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Complete physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Symptom-directed physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sexual Maturity Rating</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Laboratory Evaluations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG (females only)⁵</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hematology</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Chemistries</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
</tr>
<tr>
<td>Plasma for genotypic and phenotypic resistance testing⁶</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
<td>6 mL</td>
</tr>
<tr>
<td><strong>Pharmacology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Sampling⁷</td>
<td>2-4 mL</td>
<td>2-4 mL</td>
<td>2-4 mL</td>
<td>2-4 mL</td>
<td>2-4 mL</td>
<td>2-4 mL</td>
</tr>
<tr>
<td>Total maximum blood volume</td>
<td>19-21 mL</td>
<td>19-21 mL</td>
<td>19-21 mL</td>
<td>19-21 mL</td>
<td>17-21 mL</td>
<td>14-18 mL</td>
</tr>
</tbody>
</table>

Notes: X – required

1) Target dates and visit windows may vary per visit. See Section 6.5 for LSFU study visits, procedures, and target dates, and target visit windows associated with each visit.

2) Participants completing the Cohort 1 Step 2 Week 16 visit will not complete the 4 Weeks Post-Last Injection visit.

3) See Sections 6.5.5 and 6.7 for more details on conducting Early Termination visits. Cohort 1 Step 1 and Cohort 2 Step 3 participants completing an Early Termination visit will not have a PK evaluation performed and a PK sample will not be collected.

4) Only a sub-set of participants will conduct the qualitative phone interview. See Section 11 for qualitative interview window and details on participant selection.

5) Pregnancy testing will not be required for participants who are currently pregnant.

6) Plasma collected at the Confirmation of Virologic Failure visit for genotypic and phenotypic resistance testing will be shipped per the LPC for testing. Plasma samples collected at all other visits for genotypic and phenotypic resistance testing will be stored for testing as requested by the team. See Section 6.16 and the LPC for more details.

7) See Sections 6.5 and 6.6 for PK sample collection timepoints and windows. Cohort 1 Step 2 participants being followed per the LSFU visit schedule will have 2 mL collected for each PK sampling timepoint, whereas Cohort 2 Step 4 participants being followed per the LSFU visit schedule will have 4 mL collection for each PK sampling timepoint.
Appendix II: Sample Parental Informed Consent Forms

Appendix II-A: Sample Parental Informed Consent Form for Participation in Cohort 1 for parents/guardians of adolescents who cannot provide independent informed consent for study participation

IMPAACT 2017

Version 2.0, dated 16 August 2018

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

Your child is being asked to take part in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide that your child will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the study

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and [insert site name]. The person in charge of the study at [insert site name] is [insert name of IoR].

The study is being done to test two anti-HIV medicines (antiretrovirals or ARVs) in adolescents 12 to less than 18 years old who have HIV. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV). HIV is the virus that causes AIDS.

The study will include up to 155 adolescents from the United States. There will be two groups of adolescents, called Cohort 1 and Cohort 2. This form is about Cohort 1. Participants in Cohort 1 will be in the study for at least 16 weeks (4 months) and then up to an additional 48 weeks (12 months) as part of long-term follow-up, for a total of 64 weeks (16 months).

The United States National Institutes of Health and the company that makes CAB and RPV, ViiV Healthcare, are paying for this study.

1. The study is testing CAB and RPV in adolescents.

People with HIV usually take a combination of ARVs daily to stay healthy. There are not as many ARVs available for adolescents as for adults because many ARVs have not yet been tested in adolescents. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV when taken as pills and when given as shots in adolescents. The pills are taken every day. The shots are given every 4
weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer to have the shots rather than taking pills.

RPV pills (25mg taken once daily) have been shown to be safe and effective for both adults and adolescents 12 years and older with HIV. These pills are already approved by the US Food and Drug Administration (FDA) for adults and adolescents with HIV.

RPV shots (600mg), CAB pills (30mg), and CAB shots (400mg) are now being tested in adults with HIV. This will be the first study of these ARVs in adolescents. So far, the testing in adults has shown that RPV shots, CAB pills, and CAB shots work as well as other ARVs that are approved. However, because these ARVs are still being tested, there may be some effects that we do not know about yet.

This study will test the effects of these ARVs in adolescents. The study will look at whether these ARVs:

- Are being given at the correct dose for adolescents
- Are safe and well-tolerated
- Can control HIV in adolescents as well as other ARVs

The study will also look at how willing adolescents are to take these ARVs.

Cohort 1 of this study will be done first to test CAB and RPV pills when taken for about 1 month followed by CAB and RPV shots when taken for about 2 months. Adolescents in Cohort 1 will take either CAB pills followed by CAB shots or RPV pills followed by RPV shots. They will keep taking their usual ARVs (see #8 below for more information). If the results from Cohort 1 show that CAB pills, CAB shots and RPV shots are safe and that the dose is correct, Cohort 2 will start. Cohort 2 will test whether CAB pills and RPV pills taken together, followed by CAB and RPV shots taken together are safe and can control HIV when adolescents stop taking their previous ARVs. Some adolescents from Cohort 1 may be eligible to also take part in Cohort 2. More information about the study and CAB and RPV is given in the rest of this form.

2. Only adolescents who are eligible can participate in the study.

If you decide to allow your child to join the study, we will first do some tests to find out if your child is eligible. More information about the tests is given in #4 (see below). If your child is eligible, they will be entered in the study. If your child is not eligible, they cannot be entered in the study.

3. It is your decision whether or not your child joins the study.

Deciding to join the study is voluntary (your choice). You may choose to allow your child to join or not join. Your child will also be asked if they want to join the study. You and your child must both agree. If you allow your child to join, you can change your mind and take your child out of the study. If your child does decide to join, they can also change their mind and stop being in the study at any time. Your and your child’s choices will have no effect on the medical care your child would normally receive. Your child’s access to services, and the benefits and rights your child normally has, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

No matter what you decide about the study, it is important for your child to keep taking ARVs. This is the best known way for your child to stay healthy.
Finding out if your child is eligible

4. We will ask questions, examine your child, and discuss the study requirements with you.

To find out if your child is eligible for the study, we will:

- Review your child’s medical records.
- Ask questions about your child, your child’s health, and the medications your child takes.
- Talk with your child about birth control (ways to prevent pregnancy).
- Talk with you about the study requirements and if your child is able to meet these requirements.
- Do a physical exam. This will include looking at your child’s genitals to see the stage of development. For girls, this will also include looking at the breasts.
- Do an electrocardiogram (ECG). This is to test how well your child’s heart is working.
- Draw between 17-23mL (about 3-5 teaspoons) of blood for tests. The tests will:
  - Check your child’s blood cells.
  - Check how well your child’s liver and kidneys are working.
  - Confirm that your child has HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
  - Check the amount of HIV in your child’s blood. This is called the HIV viral load.
  - Some blood will be saved for later testing for resistance to ARVs. This test shows whether different ARVs may work against the HIV in your child’s blood.

These procedures will take about 4 hours [here and throughout this form, sites may modify the expected visit duration as needed].

5. For girls, we will also test for pregnancy.

Girls in this study cannot be pregnant. Girls should not join this study if they are pregnant or intend to become pregnant within 30 days after stopping the study ARV pills or within 48 weeks after stopping the study shots. Because the effects of the study ARVs on unborn babies are unknown, your child should not become pregnant while in this study. For all girls in the study, we will collect urine or blood to test for pregnancy.

There are certain effective methods of birth control that girls who are able to become pregnant must use while in this study. These effective methods must be continued for 30 days after stopping the study ARV pills, or for at least 48 weeks after stopping the study ARV shots. Girls who are able to become pregnant must agree to use these methods in order to take part in the study. We will help make sure your child can get effective methods by providing them here in the clinic or offering a referral. At study visits when your child will receive study medicines (either the pill or shot), we will need to confirm that your child is using effective birth control before giving her the study medicines.

Girls who become pregnant during the study will stop taking the study medicines and enter the long-term safety follow-up phase of the study (see #16 below). We will contact you and your child to find out the outcome of the pregnancy even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with your child in private, without parents/guardians present. Your child must give us permission before we can share these results with you. If the test shows that she is pregnant, we will give your child information on where medical care and other services can be received.]
If your child is pregnant, your child’s doctor may report their pregnancy to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry assists patients and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about your child, such as name, initials, contact information, or date of birth.

6. **We will tell you if your child is eligible.**

We will give you the results of all procedures and explain the results to you. We will tell you about getting care, treatment and any other services your child may need. While waiting for the results, it is important for your child to keep taking their usual ARVs.

If your child is not eligible for the study for any reason, we will tell you this. Your child will not be entered in the study. Your child can and should continue to receive medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services your child may need.

If your child does not enter the study, we will still use some information collected about your child (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If your child is eligible for the study, your child will be entered into the study.

**Entering the study**

7. **If your child is eligible, your child will enter the study.**

On the day your child enters the study we will:
- Review your child’s medical records
- Talk with you about your child’s ARV use
- Talk with your child about preventing pregnancy
- Ask your child questions about what they think about CAB or RPV
- Do a physical exam.
- Draw between 20mL (about 4 teaspoons) of blood for tests. The tests will:
  - Check your child’s blood cells.
  - Check how well your child’s liver and kidneys are working.
  - Check how much the virus has affected your child’s ability to fight the virus. This is called CD4 cell count.
  - The tests will check your child’s HIV viral load. Some blood will also be saved for later resistance testing.
- For girls, we will collect urine or blood for a pregnancy test.

At the study entry visit we may also do an ECG to look at your child’s heart. This will only be needed if your child enters the study more than 2 weeks after their first visit.

At this visit, your child will start taking CAB or RPV pills. We will give you the pills and explain how to take them. Your child will take their first dose at the visit. **Your child will continue taking their usual ARVs.**

This visit will take about 4 hours.

**Being in the study**

8. **After entering the study, participants take CAB or RPV pills for 4-6 weeks and then switch to CAB or RPV shots.**
For participants in Cohort 1, there are three phases of the study. All participants will take part in Cohort 1-Phase 1. Only those who are eligible will take part in Cohort 1-Phase 2. Participants who take part in Cohort 1-Phase 2 will also take part in Cohort 1-Phase 3, called the long-term follow-up safety phase.

In Cohort 1-Phase 1, your child will keep taking their usual ARVs. Your child will also take either CAB or RPV pills. Whether your child takes CAB or RPV will be based on the type of usual ARVs they take. The pills must be swallowed whole. They cannot be broken or crushed. They should be taken with food. This phase lasts for about 4-6 weeks. Your child will have 2 visits during this time. At these visits, we will check on how your child is doing while taking the pills (see #9 for more information). We will also check on whether your child is eligible for Cohort 1-Phase 2.

If your child is eligible for Cohort 1-Phase 2, your child will keep taking their usual ARVs. Your child will stop taking the CAB or RPV pills and start getting either CAB or RPV shots. The ARV your child gets in the shot will be the same ARV they were taking by pill. The shots are long-acting, meaning the medicine stays in the body for a long time. This phase lasts about 12 weeks. Your child will have 8 visits during this time and will get shots at three of these visits. Each shot is about 3mL (about 1 teaspoon). The shots are given in the buttocks (bottom “cheeks”). At each of these three visits, your child will be given one shot of CAB or one shot of RPV. At all of the Phase 2 visits, we will check on how your child is doing while getting the shots (see #11 for more information).

After Cohort 1-Phase 2, your child will then take part in the long-term follow-up safety phase of the study. This phase lasts about 48 weeks. Your child will keep taking their usual ARVs. There will be 4 or 5 visits during long-term follow up (see #16 for more information).

9. In Cohort 1-Phase 1, your child will have 2 visits.

Visits in this phase will be scheduled 2 weeks apart. [Sites to modify] Each visit will take about 1-3 hours. At each of these visits, we will:

- Review your child’s medical records.
- Talk with you about your child’s ARV use.
- Do a physical exam.
- Talk with your child about preventing pregnancy.
- For girls, we will also collect urine or blood to test for pregnancy.
- Remind your child to bring the oral CAB or oral RPV to the study clinic.

At two of these visits (Week 2 and Week 4a), we will draw about 5mL (about 1 teaspoon) of blood for tests. These tests will check your child’s blood cells and how well your child’s liver and kidneys are working.

At the second visit (Week 2), we will also draw about 12mL (about 2-3 teaspoons) blood for tests. This test will check your child’s HIV viral load. Some blood will be saved for later resistance testing.

At the second visit (Week 2), we will also do an intensive pharmacokinetic (PK) test. This is a test to look at the amount of CAB or RPV in your child’s blood. At this visit, we will ask you when your child took CAB or RPV in the past three days. [Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection.] For three days before this visit, you must be sure to give your child CAB or RPV on time and in the morning. This is very important. We will help you remember this before the visit.
If your child is taking oral CAB, we will need to draw your child’s blood seven times during the visit, before and after taking CAB. We will also remind you **not** to give your child CAB before coming to this visit. When you come to the visit, we will draw your child’s blood, then your child will take CAB, and then we will draw your child’s blood 6 more times, about 1, 2, 3, 4, 8 and 24 hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 14mL (about 3 teaspoons).

If your child is taking oral RPV, we will need to draw your child’s blood four times during the visit, before and after taking RPV. We will remind you **not** to give your child RPV before coming to this visit. When you come to the visit, we will draw your child’s blood, then your child will take RPV, and then we will draw your child’s blood 3 more times, about 4, 8 and 24 hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 8mL (about 2 teaspoons).

[Sites: modify language as appropriate to indicate procedures for the intensive PK collection. For the intensive PK tests, a small plastic tube will be placed in your child’s arm to draw blood samples. This tube is attached to a plastic needle so that we can draw blood several times. We will not need to stick your child with a needle each time. The plastic tube may stay in place for the blood draws in the first 24 hours.]

[Sites: modify language as appropriate to indicate procedures for intensive PK visit and overnight stays – You and your child may need to stay at the clinic or hospital for up to 24 hours. If the study clinic is able, you may be allowed to stay at the clinic the night before and during your first PK visit.]

10. **We will tell you if your child is eligible for Cohort 1-Phase 2.**

At the Week 4b visit, we will determine if your child is eligible for the second phase. At this visit we will:
- Review your child’s medical records.
- Talk with you about your child’s ARV use.
- Do a physical exam.
- Ask your child questions about what your child thinks about CAB or RPV.
- Talk with your child about preventing pregnancy.
- Draw about 12mL (about 2-3 teaspoons) blood for tests. These tests will check your child’s HIV viral load. Some blood will be saved for later resistance testing.
- For girls, we will also collect urine or blood to test for pregnancy.
- Remind your child to bring the oral CAB or oral RPV to the study clinic.
- [Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection. Remind your child to take his/her oral CAB or oral RPV in the morning for the three days before this visit.]

If your child is **not** eligible, your child will stop taking oral CAB or oral RPV and will complete a final study visit about 4 weeks after your last oral dose (see #15 for more information).

If your child is eligible for Cohort 1-Phase 2, they will continue taking their usual ARVs. Your child will take their last dose of oral CAB or oral RPV at the Week 4b visit. We will also give your child the first shot of CAB or the first shot of RPV at the Week 4b visit. We will remind you **not** to give your child oral CAB or oral RPV before coming to this visit. Your child will take oral CAB or oral RPV at the study clinic before the first shot of CAB or the first shot of RPV.

At this visit, we will also look closely at the amount of CAB or RPV in your child’s blood. To do this, we will need to draw your child’s blood two times during the visit, before taking oral CAB or RPV and after getting a shot of CAB or RPV. When you come to the visit, we will draw your child’s blood, then your child will take their
oral CAB or RPV and get a shot of CAB or RPV, and then we will draw your child’s blood again, about two hours later. Each time we will draw 2mL (less than 1 teaspoon) for a total of 4mL (less than 1 teaspoon).

11. In Cohort 1-Phase 2 your child will have 8 visits (Weeks 4b-16).

The first visit in Cohort 1-Phase 2 will be the Week 4b visit, which is described in #10 above. The other visits in this phase will be scheduled 1-3 weeks apart. [Sites to modify] Each visit will take about 1-3 hours.

At each of these visits, we will:
- Review your child’s medical records.
- Talk with your child about preventing pregnancy
- Do a physical exam. At the Week 16 visit, this will include looking at your child’s genitals to see the stage of development. For girls, this will also include looking at the breasts.

At each of these visits we will look at the amount of CAB or RPV in your child’s blood. At 6 of these visits (Week 5, 6, 8, 13, 14, 16), we will draw about 2mL of blood (less than 1 teaspoon) to do this. At the Week 12 visit, we will look very closely at the amount of CAB or RPV in your child’s blood. To do this, we will need to draw your child’s blood two times during the visit, before and after getting a shot of CAB or RPV. When you come to the visit, we will draw your child’s blood, then your child will get a shot of CAB or RPV, and then we will draw your child’s blood again, about two hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 4mL of blood (less than 1 teaspoon).

At 5 of these visits (Weeks 5, 8, 12, 13 and 16) we will also draw about 5mL of blood (about 1 teaspoon) for tests. These tests will check your child’s blood cells and how well your child’s liver and kidneys are working.

At 3 of these visits (Weeks 8, 12 and 16) we will also draw about 12mL of blood (about 2-3 teaspoons) for other tests. These tests will check your child’s HIV viral load. Some blood will be saved for later resistance testing. We will ask your child questions about getting shots of CAB or RPV.

At 1 of these visits (Week 16), we will also draw about 8mL of blood (between 1 and 2 teaspoons) for tests. These tests will check your child’s blood cells and CD4 count.

At 2 of these visits (Weeks 13 and 16) we will also do an ECG to look at your child’s heart.

At 2 of these visits (Weeks 8 and 12) we will also give your child a shot of either CAB or RPV.

At 2 of these visits (Weeks 8 and 16) we will also talk with you about your child’s ARV use.

For girls, at 3 of these visits (Weeks 8, 12 and 16) we will also collect urine or blood to test for pregnancy.

Up to two weeks after the Week 8 visit, we will contact you by phone (call or text you) to see how your child is doing after the shot of CAB or RPV. You can also contact us if you have any questions or concerns. If your child has any side effects, we will give you advice on how to manage them. We may also ask you to come back to the clinic so we can see your child in person. See #22 and 23 (below) for more information about side effects.

12. In-depth phone interview

We are very interested to understand what adolescents think about getting their ARV’s as shots. Your child will be asked if they would like to complete an in-depth phone interview. If your child would like to take part in the interview, then your child may be contacted to have the interview after getting the first shot of CAB or RPV.
If contacted, this interview will take approximately 1-2 hours, and will ask about how your child feels about having shots of CAB or RPV. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about them receiving the shots. The interview may take place at or in between the Week 4b, 5, 6, 8, and 12 study visits, or during the long-term follow-up safety phase. The interview will only take place once. The interview will be audio recorded and written down in a report. Your child’s name will not be included in the report. Not all participants will be contacted for the interview. Your child does not have to do the interview to take part in this study.

13. We will tell you if your child is eligible for Cohort 2.

After your child’s last visit in Cohort 1-Phase 2, we will tell you if your child is eligible for Cohort 2 or if your child needs additional tests to see if they qualify for Cohort 2.

If your child is not eligible for Cohort 2, or if Cohort 2 is not ready, your child will stop getting shots of CAB or RPV and will enter Cohort 1-Phase 3, also called the long-term follow-up safety phase (see #16 for more information). We will let you know when Cohort 2 is ready and if your child needs additional tests to see if they qualify for Cohort 2.

If your child is eligible for Cohort 2, and when Cohort 2 is ready, they can enter into Cohort 2.

14. Adolescents may have an extra visit if their HIV is not controlled.

Participants will have viral load tests at almost all visits to check the amount of HIV in the blood. If tests show that the viral load is higher than expected (above 200 copies/mL) your child will have repeat testing. This may occur as part of another study visit or may occur as an extra study visit.

The extra visit will take about 1-2 hours. At this visit we will:

- Review your child’s medical records.
- Do a physical exam.
- Draw about 14mL (about 3 teaspoons) of blood for tests. The tests will:
  - Check your child’s HIV viral load.
  - Check the amount of CAB or RPV in the blood.
  - We will save some blood for later resistance testing.
- Talk with your child about preventing pregnancy.
- For girls, we will also collect urine or blood to check for pregnancy.

If the repeat test also shows an increased amount of HIV in your child’s blood, your child will stop taking the study product. If your child was getting shots of CAB or RPV, your child will enter long-term follow-up (more information in #16 below).

15. If your child is not eligible to receive shots of CAB or RPV your child will stop the study early.

If your child is not eligible to get shots of CAB or RPV in Cohort 1, your child will stop taking oral CAB or oral RPV and will complete a final study visit about 4 weeks after your child’s last oral dose.

During this visit, we will:
• Review your child’s medical records.
• Do a physical exam. This will include looking at your child’s genitals to see the stage of development. For girls, this will also include looking at the breasts.
• Draw blood for tests. This would be about 17mL of blood (about 3-4 teaspoons) for these tests. These tests will check:
  o Your child’s blood cells.
  o How well your child’s liver and kidneys are working.
  o Your child’s HIV viral load.
  o Some blood will be saved for future resistance testing.
• Talk with your child about preventing pregnancy.
• For girls, we will also collect urine or blood to check for pregnancy.
• Ask your child questions about taking CAB or RPV.
• We will also talk with you about your child’s ARV use.

16. If your child is not eligible to enroll in Cohort 2, or if Cohort 2 is not yet open, your child will enter Cohort 1-Phase 3, also called the long-term follow-up safety phase.

If your child is not able to enroll in Cohort 2 after getting shots in Cohort 1-Phase 2, or if Cohort 2 is not yet open, your child will enter a long-term follow-up safety phase after the last shot of study product. At this time, your child will stop getting shots of CAB or RPV. If your child becomes pregnant, she will enter this phase of the study after her last dose of study medicine, whether the pill or the shot. Your child will keep taking their usual ARVs. There will be 4 or 5 additional visits during the long-term follow-up.

These visits will be scheduled 4, 12, 24, 36 and 48 weeks after your child’s last shot of CAB or RPV. Each of these visits will take about 1-3 hours. At these visits, we will:
• Review your child’s medical records.
• Do a physical exam. At the final long-term follow-up visit, this will include examination of your child’s genitals to see the stage of development. For girls, this will also include looking at the breasts.
• Talk with your child about preventing pregnancy.
• Draw blood for tests. This would be about 19mL of blood (about 4 teaspoons) for these tests. These tests will check:
  o Your child’s blood cells.
  o How well your child’s liver and kidneys are working.
  o Your child’s HIV viral load.
  o The amount of CAB or RPV in the blood.
  o Some blood will also be saved for future resistance testing.
• For girls, we will also collect urine or blood to check for pregnancy.
• At two of these visits (4 weeks and 48 weeks after your child’s last shot of CAB or RPV) we will talk with you about your child’s ARV use.
• At the final visit (48 weeks after your child’s last shot of CAB or RPV), we will also ask your child questions about getting shots of CAB or RPV.

For participants who complete the Week 16 visit in Cohort 1-Phase 2, the first long-term follow-up visit will be skipped entirely. The Week 16 visit and the first long-term follow-up visit are very similar and do not need to be conducted twice.
17. The tests for the amount of CAB or RPV in your child’s blood will be done at different laboratories.

We will do most of the tests of blood or urine here at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals for your child as needed.

We will also draw blood to check the amount of CAB or RPV in your child’s blood. This is called a pharmacokinetic (PK) test. The test will be done at other laboratories in the United States or in Ireland. We will not usually give you the results of this test during the study.

18. We may take your child off of the study.

We may take you off the study ARVs if:
• Your child is not able to come to the study visits or we determine that your child cannot meet the study requirements.
• Your child is not able to take the study ARVs.
• The study ARVs are not controlling the HIV in your child’s blood.
• Continuing the study ARVs may be harmful to your child.
• You request to stop the study ARVs for your child.

If your child stops the oral study ARVs early, we will ask you to come back to the clinic with your child about four weeks after they stop the oral study ARVs (see #15 above). Your child will not have any other visits after this.

If your child stops the ARV shots early, we will ask you to come back to the clinic with your child for four to five additional study visits for long-term follow-up (see #16 above). Your child will not have any other visits after these four or five visits.

We may also take your child off the study early if the study is stopped for any reason.

The study cannot provide other types of ARVs, but we will give information, counseling, and referrals to where your child can get care and treatment needed. We will help make sure your child can get ARVs from outside of the study. If the study stops early, every effort will be made to make certain that there is no interruption in your child’s therapy.

19. Please tell us if your child wants to leave the study.

Your child is free to leave the study at any time for any reason. The care that your child receives at this clinic will not be affected, but it is important for us to know about your decision.

If your child stops the study ARVs, we may ask you to return to the study clinic with your child for additional study visits described in #15 and #16 above. If your child stops the study early, we may ask that your child has one final study visit.

We will answer any questions you or your child may have and give you information on how to contact us in the future, if you wish.
**Risks of the study**

Taking part in this study may involve some risks and discomfort. The risks are different for each phase of the study. Cohort 1-Phase 1 risks include: risks from blood draws, risks from the study pills (CAB or RPV), and risks to your child’s privacy.

Cohort 1-Phase 2 risks include: risks from blood draws, risks from receiving the injection, risks from the study pills (CAB or RPV) and the study shots (long-acting CAB or RPV) and risks to your child’s privacy.

Cohort 1-Phase 3 risks include: risks from blood draws, and risks to your child’s privacy.

20. **Risk from blood draws**

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

21. **Risk from receiving the injection**

People in other studies who have received the CAB LA and RPV LA shots said they had pain, skin irritation, skin redness, bumps, swelling, itching, bruising at the spot where they got the shot. Most reactions go away in a week or less but sometimes they can last a long time. Most people usually do well with them and rarely need to stop the drug.

The shots will be given in the muscles of your child’s buttocks. The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve.

The risks of this are not well understood, but could make drug levels too low or too high. If too low, the drug may not work against your child’s HIV. If RPV is too high, there could be a change in your child’s heart beat, which in severe cases can be life-threatening. Everything possible will be done to decrease this risk, including watching your child for problems during the study. If your child’s doctor thinks that the injection was not given the right way, your child might be asked to stay in the clinic up to [sites to modify] 2 hours after the injection to watch how your child is doing and extra tests may be needed to be sure your child is safe. If you or your child are worried about this risk, talk to your child’s doctor.

22. **There are risks from the study ARVs**

All ARVs can cause side effects. This includes the ARVs your child is currently taking and the ARVs that are given in the study. Some side effects are minor; others can be severe. Some side effects are common; others are rare. Some people who take ARVs have some of the side effects. Other people have different side effects, or no side effects.

The most common and most serious side effects of the study ARVs, CAB and RPV, are listed below. This is based on what we know now about CAB and RPV. There may be other side effects that we do not know about now. This may be especially true for adolescents, because this is the first study of CAB and RPV in adolescents.

This form does not list all possible side effects of all ARVs. If your child joins the study, we will tell you more about the ARVs your child will be taking. At each study visit, we will check on whether the ARVs may be causing side effects. We will also tell you what to do if your child has side effects. If you or your child have questions or concerns at any time, please tell us.
23. Some side effects from the CAB pills and the CAB LA

Many people have received CAB pills or the CAB LA shot in other studies. The table below lists side effects from other studies of CAB with people who have HIV. It is not known if CAB, other drugs or the patient’s other health problems caused or affected these. Some of these are the same side effects as RPV (see #24 below).

### Common Side Effects of CAB

<table>
<thead>
<tr>
<th>Very Common Side Effects of CAB</th>
<th>Common Side Effects of CAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea (feeling sick to the stomach)</td>
<td>• Rash</td>
</tr>
<tr>
<td>• Diarrhea or loose stools</td>
<td>• Itching</td>
</tr>
<tr>
<td>• Runny nose, sore throat/Upper respiratory tract infection</td>
<td>• Vomiting (being sick)</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Stomach pain and discomfort</td>
</tr>
<tr>
<td>• Fever</td>
<td>• Problems sleeping</td>
</tr>
<tr>
<td>• Lack of energy</td>
<td>• Abnormal dreams/nightmares</td>
</tr>
<tr>
<td></td>
<td>• Feeling light headed</td>
</tr>
<tr>
<td></td>
<td>• Depression</td>
</tr>
<tr>
<td></td>
<td>• Passing gas or wind</td>
</tr>
<tr>
<td></td>
<td>• Joint or muscle pain</td>
</tr>
<tr>
<td></td>
<td>• Increase in the level of enzymes made in the muscles (creatine phosphokinase)</td>
</tr>
</tbody>
</table>

The following effects have also been seen in some of the people who received CAB pills or the CAB LA shot in other studies:

#### Abnormal liver tests:

A small number of people across all studies (just over 1% of 1644 participants as of April 2017) had abnormal liver tests requiring them to stop CAB. Some abnormal liver tests were explained by other things such as a new virus infection, like Hepatitis A, B or C. Very few people did not have another possible reason so it is possible that a mild form of liver damage happened from taking CAB. The liver tests got better after stopping CAB, showing that any damage was temporary.

Blood tests to check the health of your child’s liver will be done during the study. Your child’s study doctor will tell you if your child needs to stop taking the study drugs or if other action is needed. If your child stops taking the study drug, they may be able to re-start the study drug or they may need to change their usual ARVs.

#### Seizures/convulsions:

Seizures have been seen (rarely) in people with and without HIV. They are not thought to be caused by CAB, but the study staff will ask you about them.

In other studies, two people without HIV had a history of seizures (epilepsy), and had a seizure about 3 months and 9 months after starting CAB. One other person with HIV but without a history of seizures, had seizures about one year after starting CAB. This participant had a long period of seizures without medical treatment and died. It
is not known if CAB was part of the reason for seizures in these people. If your child has a history of seizures, please let your child’s study doctor know.

24. Some side effects from the RPV pills and the RPV LA

The following side effects have been seen with rilpivirine in HIV-infected patients in clinical trials. Oral RPV (Edurant) is a marketed drug and many more people have received Edurant. The side effects of Edurant are more known than the side effects for CAB, and more known than the side effects of RPV LA. Many people have taken part in studies and received RPV LA, and some also received CAB LA. The following side effects have been seen in studies in people with HIV taking RPV.

### Common Side Effects of RPV

<table>
<thead>
<tr>
<th>Very Common Side Effects of RPV</th>
<th>Common Side Effects of RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems sleeping</td>
<td>Rash</td>
</tr>
<tr>
<td>Headache</td>
<td>Depression</td>
</tr>
<tr>
<td>Feeling light headed</td>
<td>Abnormal dreams</td>
</tr>
<tr>
<td>Nausea (feeling sick to the stomach)</td>
<td>Lack of energy</td>
</tr>
<tr>
<td>Increase in the level of liver enzymes</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Sleepiness</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Stomach pain and discomfort</td>
</tr>
<tr>
<td></td>
<td>Dry Mouth</td>
</tr>
<tr>
<td></td>
<td>Sleep problems</td>
</tr>
</tbody>
</table>

The following effects have also been seen in some of the people who received RPV in other studies:

**Abnormal blood tests:**

Other changes in blood tests have also been observed. People with hepatitis B or C or increased in liver tests showing possible liver damage before starting RPV may have worse liver tests while taking RPV. A few cases of liver problems have also been seen in people taking RPV who did not already have any liver problems.

Sometimes allergic reactions can affect body organs, like the liver and cause liver problems which can lead to liver failure. Contact your child’s study doctor right away if your child has any of the following signs or symptoms of liver problems:

- **Yellowing of the skin or whites of the eyes**
- **Dark or tea colored urine**
- **Pale colored stools/bowel movements**
- **Nausea/vomiting**
- **Loss of appetite**
- **Pain, aching or tenderness on the right side below the ribs**
Blood tests to check the health of your child’s liver will be done during the study. Your child’s study doctor will tell you if your child needs to stop taking the study drugs or if other action is needed. If your child stops taking the study drug, they may be able to re-start the study drug or they may need to change their usual ARVs.

**Skin Rash:**

Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most of rashes got better after one week, and the people did not need to stop taking RPV. However, the study ARVs will need to be stopped for some types of moderate rash and all types of severe rash, which can be life-threatening. If this happens to your child, they will need to come for extra study visits to monitor their health. Some people with rash may also have other signs and symptoms of allergic reaction.

If your child has any type of rash or other skin problems during the study you must tell your child’s study doctor right away, and the doctor may tell your child to stop taking CAB and/or RPV.

25. **There may be other possible risks from the study ARVs.**

*The study ARV shots stay in your body for a long time*

The shots your child gets in this study are long acting, meaning they stay in your child’s body for a long time. In most people, the drugs will no longer be in the body one year after an injection, while in some people low levels of CAB and RPV may still be in the body after one year. If your child develops a side effect to the study drug after the shot, there will be no way to remove the drug from your child’s body. If your child gets a shot of CAB or RPV, we will monitor their health for 48 weeks after their last shot. If your child develops a symptom from these drugs while the drugs are still in their body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

While the amount of study drugs in your child’s body decrease slowly over time after they stop getting shots the study drugs could stop working against your child’s HIV. When stopping long acting HIV drugs, it will be very important to start taking other HIV medications, as your child’s study doctor tells you, so your child’s HIV medications do not stop working against their HIV.

*Risk of resistance*

All ARVs can cause some resistance if not taken correctly. Resistance means that the ARVs may not work against HIV if these ARVs are taken again in the future. To stop resistance, it is important that your child takes the ARVs as instructed, and does not miss any doses.

*Effects on other ARVs*

We do not expect the study ARVs to change the way other ARVs work in the body. For example, if your child was to join the study, we would expect the ARVs your child is currently taking to keep working to control the amount of HIV in their body. We also do not expect the study ARVs to cause more or worse side effects from other ARVs. However, this study is being done to learn more about these kinds of possible effects.

*Mental Illness*

Some people with HIV sometimes have feelings of depression or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with drugs called integrase inhibitors [INIs] for HIV like CAB, have had suicidal thoughts and actions, particularly patients with a prior history of depression or mental health illness.
Tell the study doctor if your child has a history of mental health illness. If your child has thoughts of hurting or killing their self or have any other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

**Possible effects on pregnancy or unborn babies**

HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if CAB or RPV are safe in pregnancy.

There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug.

Early results from one large study in Botswana showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects of the brain or spine in the new baby. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.

CAB is not the same drug as DTG. We do know that CAB and DTG belong to the same class of medications and work in a similar way to treat HIV infection. We do not know if CAB can cause brain or spine defects in babies.

Girls who are able to become pregnant must agree to use certain effective methods of birth control to be in this study (see #5 above). If your child becomes pregnant during the study, please let us know right away.

**Immune reconstitution syndrome**

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases may occur soon after starting combination ARVs but can also occur later. Some of these symptoms may be life threatening. If your child starts having new symptoms, or if you notice that any of your child’s existing symptoms are getting worse after starting the ARVs, tell your child’s doctor immediately.

**Abnormal placement of body fat and wasting**

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement
26. There could be risks of disclosure of your child’s information.

We will make every effort to keep your child’s information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your child’s name will be written on some records.

Despite our best efforts to keep your child’s information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly. Your child could feel stress or embarrassment.

To help us protect your child’s privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify your child, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify your child. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your child’s participation in the study to others, if you wish.

Benefits of the study

27. There may be a direct benefit to your child from being in the study.

By joining the study, your child will be part of the search for ARVs that may be better for adolescents. We do not know if being in the study will benefit your child in any way. There may be a direct benefit to your child by taking part in this study, but no guarantee can be made. For example, the study drugs may lower the amount of HIV in the blood. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. It is also possible that your child may receive no direct benefit from this study. Information learned from this study may help other adolescents who have HIV.

Your child will have regular visits here and frequent checks on your child’s health, including tests for the amount of HIV in your child’s blood, called viral load. It is possible that the study ARVs will slow your child’s HIV infection. Information learned from this study may help other adolescents with HIV.

Other information about the study

28. There are no costs from being in the study.

There are no costs to you for study visits, CAB, RPV or procedures.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).]

29. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:
- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
• Other U.S., local, and international regulatory entities
• The IMPAACT Network that is coordinating the study
• ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child’s name or identify your child personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

Your child’s study information may be given to other authorities if required by law. [Sites add more specific detail here as needed; example follows:] For example, we are required to report any significant risk of harm to your child or others.

30. If your child gets sick or injured, contact us immediately.

Your child’s health is important to us. We will make every effort to protect your child’s well-being and minimize risks. It is possible, however, that your child could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat your child or tell you where your child can get treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through [site name or] the U.S. National Institutes of Health.

Whom to contact

31. If you have questions, concerns, or problems at any time, use these contacts.

• If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

• If you have questions about your child’s rights as research participants or concerns about how your child is being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

• If your child has any health or other problems that may be related to study participation:
  [insert name and telephone number of investigator or other study staff]

• If you want your child to leave the study:
  [insert name and telephone number of investigator or other study staff]
**Signatures**

If you agree to allow your child to participate in this study, please sign or make your mark below.

Before deciding whether to allow your child to participate in this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of your child if you decide to allow your child to join.

If you decide to allow your child to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time. If you want the results from this study, please tell the study staff.

You do not give up any rights by signing this form.

*Insert signature blocks as required by site IRB/EC policies.*

<table>
<thead>
<tr>
<th>Name of Participant (print)</th>
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</thead>
<tbody>
<tr>
<td>Name of Parent/Guardian/ Legally Authorized Representative (print)</td>
</tr>
<tr>
<td>Name of Study Staff Conducting Consent Process Name (print)</td>
</tr>
<tr>
<td>Name of Witness (as appropriate; print)</td>
</tr>
</tbody>
</table>
Appendix II-B: Sample Parental Informed Consent Form for Participation in Cohort 2
for parents/guardians of adolescents who cannot provide independent informed consent for study participation

IMPAACT 2017

Version 2.0, dated 16 August 2018

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

Your child is being asked to take part in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide to allow your child to participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the study

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and [insert site name]. The person in charge of the study at [insert site name] is [insert name of IoR].

The study is being done to test two anti-HIV medicines (antiretrovirals or ARVs) in adolescents 12 to less than 18 years old who have HIV. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV). HIV is the virus that causes AIDS.

The study will include up to 155 adolescents from the United States. There will be two groups of adolescents, called Cohort 1 and Cohort 2. This form is about Cohort 2. Participants in Cohort 2 will be in the study for 2 to 3 years. In Cohort 2, participants will get study product for 96 weeks (about 2 years). After 96 weeks, participants will have the option to continue getting the study product. If your child chooses to continue getting the study product, your child will not have any additional study visits. If your child chooses to stop getting the study product, your child will enter long-term follow-up and continue having study visits for an additional 48 weeks (about 1 year).

The United States National Institutes of Health and the company that makes CAB and RPV, ViiV Healthcare, are paying for this study.

1. The study is testing CAB and RPV in adolescents.

People with HIV usually take a combination of ARVs daily to stay healthy. There are not as many ARVs available for adolescents as for adults because many ARVs have not yet been tested in adolescents. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV when
taken as pills and when given as shots in adolescents. The pills are taken every day. The shots are given every 4 weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer to have the shots rather than taking pills.

RPV pills (25mg taken once daily) have been shown to be safe and effective for both adults and adolescents 12 years and older with HIV. These pills are already approved by the US Food and Drug Administration (FDA) for adults and adolescents with HIV.

RPV shots (600mg), CAB pills (30mg), and CAB shots (400mg) are now being tested in adults with HIV. This will be the first study of these ARVs in adolescents. So far, the testing in adults has shown that RPV shots, CAB pills, and CAB shots work as well as other ARVs that are approved. However, because these ARVs are still being tested, there may be some effects that we do not know about yet.

This study will test the effects of these ARVs in adolescents. The study will look at whether these ARVs:

- Are being given at the correct dose for adolescents
- Are safe and well-tolerated
- Can control HIV in adolescents as well as other ARVs

The study will also look at how willing adolescents are to take these ARVs.

Cohort 1 of this study was done first to test CAB and RPV pills when taken for about 1 month followed by CAB and RPV shots when taken for about 2 months. Cohort 2 is now being done to test CAB and RPV pills taken together, followed by CAB and RPV shots taken together for up to two years. Cohort 2 will look at whether these study ARVs are safe and can control HIV when adolescents stop taking their previous ARVs. More information about the study and CAB and RPV is given in the rest of this form.

2. Only adolescents who are eligible can participate in the study.

If you decide to allow your child to join the study, we will first do some tests to find out if your child is eligible. More information about the tests is given in #4 (see below). If your child is eligible, your child will be entered in the study. If your child is not eligible, your child cannot be entered in the study.

3. It is your decision whether or not your child joins the study.

Deciding to join the study is voluntary (your choice). You may choose to allow your child to join or not join. Your child will also be asked if they want to join the study. You and your child must both agree. If you allow your child to join, you can change your mind and take your child out of the study. If your child does decide to join, they can also change their mind and stop being in the study at any time. Your and your child’s choices will have no effect on the medical care your child would normally receive. Your child’s access to services, and the benefits and rights your child normally has, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

*No matter what you decide about the study, it is important for your child to keeping taking ARVs. This is the best known way for your child to stay healthy.*
Finding out if your child is eligible

4. We will ask questions, examine your child, and discuss the study requirements with you.

To find out if your child is eligible for the study, we will:

- Review your child’s medical records.
- Ask questions about your child, your child’s health, and the medications your child takes.
- Talk with your child about birth control (ways to prevent pregnancy).
- Talk with you about the study requirements and if your child is able to meet these requirements.
- Do a physical exam. This will include looking at your child’s genitals to see the stage of development. For girls, this will also include looking at the breasts.
- Do an electrocardiogram (ECG). This is to test how well your child’s heart is working.
- Draw about 17-23mL (about 3-5 teaspoons) of blood for tests. The tests will:
  - Check your child’s blood cells.
  - Check how well your child’s liver and kidneys are working.
  - Confirm that your child has HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
  - Check the amount of HIV in your child’s blood. This is called the HIV viral load.
  - Some blood will be saved for later testing for resistance to ARVs. This test shows whether different ARVs may work against the HIV in your child’s blood.

These procedures will take about 4 hours [here and throughout this form, sites may modify the expected visit duration as needed].

5. For girls, we will also test for pregnancy.

Girls in this study cannot be pregnant. Girls should not join this study if they are pregnant or intend to become pregnant within 30 days after stopping the study ARV pills or within 48 weeks after stopping the study shots. Because the effects of the study ARVs on unborn babies are unknown, your child should not become pregnant while in this study. For all girls in the study, we will collect urine or blood to test for pregnancy.

There are certain effective methods of birth control that girls who are able to become pregnant must use while in this study. These effective methods must be continued for 30 days after stopping the study ARV pills, or for at least 48 weeks after stopping the study ARV shots. Girls who are able to become pregnant, must agree to use these methods in order to take part in the study. We will help make sure your child can get effective methods by providing them here in the clinic or offering a referral. At study visits when your child will receive study medicines (either the pill or shot), we will need to confirm that your child is using effective birth control before giving her the study medicines.

Girls who become pregnant during the study will stop taking the study medicines and enter the long-term safety follow-up phase of the study (see #15 below). We will also contact you and your child to find out the outcome of the pregnancy even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with your child in private, without parents/guardians present. Your child must give us permission before we can share these results with you. If the test shows that she is pregnant, we will give your child information on where medical care and other services can be received.]
If your child is pregnant, your child’s doctor may report their pregnancy to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry assists patients and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about your child, such as name, initials, contact information, or date of birth.

6. **We will tell you if your child is eligible.**

We will give you the results of all procedures and explain the results to you. We will tell you about getting care, treatment and any other services your child may need. While waiting for the results, it is important for your child to keep taking their usual ARVs.

If your child is *not* eligible for the study for any reason, we will tell you this. Your child will *not* be entered in the study. Your child can and should continue to receive medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services your child may need.

If your child does not enter the study, we will still use some information collected about your child (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If your child is *eligible* for the study, your child will be entered into the study.

**Entering the study**

7. **If your child is eligible, your child will enter the study.**

On the day your child enters the study we will:

- Review your child’s medical records
- Talk with you about your child’s ARV use
- Talk with your child about preventing pregnancy
- Ask your child questions about what they think about CAB and RPV
- Do a physical exam.
- Draw between 20mL (about 4 teaspoons) of blood for tests. The tests will:
  - Check your child’s blood cells.
  - Check how well your child’s liver and kidneys are working.
  - Check how much the virus has affected your child’s ability to fight the virus. This is called CD4 cell count.
  - The tests will check your child’s HIV viral load. Some blood will also be saved for later resistance testing.
- For girls, we will collect urine or blood for a pregnancy test.

At the study entry visit we may also do an ECG to look at your child’s heart. This will only be needed if your child enters the study more than 2 weeks after your child’s first visit.

At this visit, your child will stop taking their usual ARVs and start taking CAB and RPV pills. We will give you the pills and explain how to take them. Your child will take their first dose at the visit.

This visit will take about 4 hours.

**Being in the study**

8. **After entering the study, participants take CAB and RPV pills for 4-6 weeks and then switch to CAB and RPV shots.**
For participants in Cohort 2, there are three phases of the study. All participants will take part in Cohort 2-Phase 1. Only those who are eligible will take part in Cohort 2-Phase 2. Participants who take part in Cohort 2-Phase 2 will also take part in Cohort 2-Phase 3, called the long-term follow-up safety phase.

In Cohort 2-Phase 1, your child will take CAB and RPV pills. The pills must be swallowed whole. They cannot be broken or crushed. They should be taken with food. This phase lasts for about 4-6 weeks. Your child will have 2 visits during this time. At these visits, we will check on how your child is doing while taking the pills (see #9 for more information). We will also check on whether your child is eligible for Cohort 2-Phase 2.

If your child is eligible for Cohort 2-Phase 2, your child will stop taking CAB and RPV pills and start getting CAB and RPV shots. This phase lasts 2-3 years. Your child will have 25 visits over about two years and may have another 5 visits over one additional year. Your child will get shots at 23 visits during the first two years. At each of these 23 visits, your child will be given one shot of CAB and one shot of RPV. Each shot is 3mL (about 1 teaspoon). The shots are given in the buttocks (bottom “cheeks”). The shots may be given on the same side of the buttocks or on different sides. The shots are long-acting, meaning the medicine stays in your child’s body for a long time. They are given every 4 weeks. At all of these study visits, we will check on how your child is doing while getting the shots (see #11 for more information).

After Cohort 2-Phase 2, your child will have the option to continue getting the long-acting injections or to stop getting them. If your child no longer wants to get the injections, they will take part in Cohort 2-Phase 3, the long-term follow-up safety phase of the study. This phase lasts about 48 weeks. Your child will also go back to taking their usual (pre-study) ARVs. There will be 4 or 5 visits during long-term follow up (see #15 for more information).

9. In Cohort 2-Phase 1, your child will have 2 visits.

Visits in this phase will be scheduled 2 weeks apart. [Sites to modify] Each visit will take about 1-3 hours. At each of these visits, we will:

- Review your child’s medical records.
- Talk with you about your child’s ARV use
- Do a physical exam.
- Talk with your child about preventing pregnancy.
- For girls, we will collect urine or blood to test for pregnancy.
- Remind your child to bring the oral CAB and oral RPV to the study clinic.

At two of these visits (Week 2 and Week 4a), we will draw about 5mL (about 1 teaspoon) of blood for tests. These tests will check your child’s blood cells and how well your child’s liver and kidneys are working.

At the second visit (Week 2), we will draw about 12mL (about 2-3 teaspoons) blood for tests. This test will check your child’s HIV viral load. Some blood will be saved for later resistance testing.

At the Week 2 visit we will also test the amount of CAB and RPV in your child’s blood. This is called a pharmacokinetic (PK) test. At this visit, we will ask you when your child took CAB or RPV in the past three days. [Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection.] For three days before this visit, you must be sure to give your child CAB and RPV on time and in the morning. This is very important. We will help you remember this before the visit.
We will need to draw your child’s blood two times during the visit, before and after taking CAB and RPV. We will remind you to **not** give your child CAB or RPV before coming to this visit. When you come to the visit, we will draw your child’s blood, then your child will take CAB and RPV, and then we will draw your child’s blood again, about two hours later. Each time we will draw 4mL (less than 1 teaspoon), for a total of 8mL (about 2 teaspoons).

Study staff will let you know when these procedures will occur ahead of time.

**10. We will tell you if your child is eligible for Cohort 2-Phase 2.**

At the Week 4b visit, we will determine if your child is eligible for Cohort 2-Phase 2. At this visit we will:

- Review your child’s medical records.
- Talk with you about your child’s ARV use.
- Do a physical exam.
- Ask your child questions about what your child thinks about CAB or RPV.
- Talk with your child about preventing pregnancy.
- Draw about 12mL (about 2-3 teaspoons) blood for tests. These tests will check your child’s HIV viral load. Some blood will be saved for later resistance testing.
- For girls, we will also collect urine or blood to test for pregnancy.
- Remind your child to bring the oral CAB and oral RPV to the study clinic.
- **[Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection. Remind your child to take his/her oral CAB and oral RPV in the morning for the three days before this visit.]**

If your child is not eligible, your child will stop taking oral CAB and oral RPV and go back to taking their usual ARVs. If your child did not participate in Cohort 1, they will complete a final study visit about 4 weeks after their last oral dose (see #14 for more information). If your child also participated in Cohort 1 and received shots of CAB or RPV, but is not eligible to get the shots of CAB and RPV in Cohort 2, they will stop taking oral CAB and oral RPV and will enter into Cohort 2-Phase 3 long-term follow-up (see #15 below).

If your child is eligible, your child will take their last dose of oral CAB and oral RPV at the Week 4b visit. At this visit, we will also give your child the first shot of CAB and the first shot of RPV. We will remind you **not** to give your child oral CAB and RPV before coming to this visit. Your child will take oral CAB and RPV at the study clinic before the first shot of CAB and the first shot of RPV.

At this visit, we will also look closely at the amount of CAB and RPV in your child’s blood. To do this, we will need to draw your child’s blood two times during the visit, before taking oral CAB and RPV and after getting a shot of CAB and a shot of RPV. When you come to the visit, we will draw your child’s blood, then your child will take their oral CAB and RPV and get a shot of CAB and RPV, and then we will draw your child’s blood again, about two hours later. Each time we will draw 4mL (less than 1 teaspoon) for a total of 8mL (about 2 teaspoons).
11. In Cohort 2-Phase 2 your child will have 26 visits (Weeks 4b-96).

The first visit in Cohort 1-Phase 2 will be the Week 4b visit, which is described in #10 above. Most of the other visits in this phase will be scheduled about 4 weeks apart. [Sites to modify] Each visit will take about 1-3 hours. At each of these visits, we will:

- Review your child’s medical records.
- Talk with your child about prevention pregnancy.
- Do a physical exam. At two of these visits (Weeks 24 and 96), this exam will include examination of your child’s genitals to see the stage of development. For girls, this will also include looking at the breasts.

At 23 of these visits (Weeks 8-24 and 28-96) we will:
- Give a shot of CAB and a shot of RPV.
- For girls, we will also collect urine or blood to check for pregnancy.

At 16 of these visits (Weeks 5, 8-24, 28-48, 60, 72, 84, and 96) we will draw about 5mL of blood (about 1 teaspoon) for tests. These tests will check:
- Your child’s blood cells
- How well your child’s liver and kidneys are working

At 15 of these visits (Weeks 8-24, 28-48, 60, 72, 84, and 96) we will draw about 12mL of blood (about 2-3 teaspoons) for tests. These tests will check:
- Your child’s HIV viral load.
- Some blood will be saved for later resistance testing.

At 13 of these visits (Weeks 5, 8-24, 25, 36, 48, 60, 72, 84, and 96), we will also draw about 4mL of blood (less than 1 teaspoon) of blood to look at the amount of CAB and RPV in the blood.

At 4 of these visits (Weeks 24, 48, 72 and 96) we will draw about 3mL of blood (about 1 teaspoon) to check your child’s CD4 count.

At 5 of these visits (Weeks 8, 12, 24, 48, and 96) we will ask your child questions about getting the shots of CAB and RPV.

At 5 of these visits (Weeks 8, 24, 48, 72, and 96) we may also talk with you and your child about how your child is doing with the visit schedule.

At 2 of these visits (Week 48 and 96) we will also talk with your child about preventing pregnancy.

Study staff will let you know when these procedures will occur ahead of time.

12. In-depth phone interviews

We are very interested to understand what adolescents think about getting their ARV’s as shots. Your child will be asked if they would like to complete an in-depth phone interview. If your child would like to take part in the interview, then your child may be contacted to have the interview after getting the sixth shot of CAB and RPV.

If contacted, this interview will take approximately 1-2 hours, and will ask about how your child feels about having shots of CAB and RPV. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about them.
receiving the shots. The interview may take place at or in between the Week 24 through 96 visits or during the long-term follow-up safety phase. The interview will only take place once. The interview will be audio recorded and written down in a report. Your child’s name will not be included in the report. Not all participants will be contacted for the interview. Your child does not have to do the interview to take part in this study.

**13. Adolescents may have an extra visit if their HIV is not controlled.**

Participants will have viral load tests at almost all visits to check the amount of HIV in the blood. If tests show that the viral load is higher than expected (above 200 copies/mL) your child will have repeat testing. This may occur as part of another study visit or may occur as an extra study visit.

The extra visit will take about 1-2 hours. At this visit we will:
- Review your child’s medical records.
- Do a physical exam.
- Draw about 16mL (about 3 teaspoons) of blood for tests. The tests will:
  - Check your child’s HIV viral load.
  - Check the amount of CAB and RPV in the blood.
  - We will save some blood for later resistance testing.
- Talk with your child about preventing pregnancy.
- For girls, we will also collect urine or blood to check for pregnancy.

If the repeat test also shows an increased amount of HIV in your child’s blood, your child will stop taking the study product and start taking their previous ARVs again. If your child was getting shots of CAB and RPV, your child will enter long-term follow-up (more information in #15 below).

**14. If your child is not eligible to receive shots of CAB and RPV your child will stop the study early.**

If your child is not eligible to receive shots of CAB and RPV, your child will stop taking oral CAB and oral RPV and will complete a final study visit about 4 weeks after their last oral dose.

During this visit, we will:
- Review your child’s medical records.
- Do a physical exam. This will include examination of your child’s genitals to see the stage of development. For girls, this will also include looking at the breasts.
- Draw blood for tests. This would be about 17mL of blood (about 3-4 teaspoons) for these tests. These tests will check:
  - Your child’s blood cells.
  - How well your child’s liver and kidneys are working.
  - Your child’s HIV viral load.
  - Some blood will also be saved for later resistance testing.
- Talk with your child about preventing pregnancy.
- For girls, we will also collect urine or blood to check for pregnancy.
- Ask your child questions about taking the oral CAB and oral RPV.
- We will also talk with you about your child’s ARV use.

If your child also participated in Cohort 1 and received shots of CAB or RPV in Cohort 1-Phase 2, but is not eligible to get the shots of CAB and RPV in Cohort 2, they will stop taking oral CAB and oral RPV and will enter into Cohort 2-Phase 3 long-term follow-up (see #15 below).
15. If your child stops the shots of CAB and RPV early or after the Week 96 study visit, your child will enter long-term follow-up.

If your child stops the shots of CAB and RPV early, or chooses to not continue to get the shots of CAB and RPV after the final visit (Week 96) of the study, your child will enter Cohort 2-Phase 3, also called the long-term follow-up safety phase, after the last shot of study product. If your child becomes pregnant, she will enter this phase of the study after her last dose of study medicine, whether the pill or the shot. At this time, your child will stop getting shots of CAB and RPV. Your child will start taking your previous ARVs again. There will be 4 or 5 additional visits during the long-term follow up.

These visits will be scheduled 4, 12, 24, 36 and 48 weeks after your child’s last shot of CAB and RPV [Sites to modify] Each of these visits will take about 1-3 hours. At these visits, we will:
- Review your child’s medical records.
- Do a physical exam. At the final long-term follow-up visit, this will include examination of your child’s genitals to see the stage of development. For girls, this will also include looking at the breasts.
- Talk with your child about preventing pregnancy.
- Draw blood for tests. This would be about 21mL of blood (about 4 teaspoons) for these tests. These tests will check:
  - Your child’s blood cells.
  - How well your child’s liver and kidneys are working.
  - Your child’s HIV viral load.
  - The amount of CAB and RPV in the blood.
  - Some blood will also be saved for future resistance testing.
- For girls, we will also collect urine or blood to check for pregnancy.
- At two of these visits (4 weeks and 48 weeks after your child’s last shot of CAB and RPV) we will talk with you about your child’s ARV use.
- At the final visit (48 weeks after your child’s last shot of CAB and RPV), we will also ask your child questions about getting shots of CAB and RPV.

For participants who complete the Week 16 visit in Cohort 2-Phase 2, the first long-term follow-up visit will be skipped entirely. The Week 16 visit and the first long-term follow-up visit are very similar and do not need to be conducted twice.

16. The tests for the amount of CAB and RPV in your child’s blood will be done at different laboratories.

We will do most of the tests of blood or urine here at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals for your child as needed.

We will also draw blood to check the amount of CAB and RPV in your child’s blood. This is called a pharmacokinetic (PK) test. The test will be done at other laboratories in the United States or in Ireland. We will not usually give you the results of this test during the study.

17. We may take your child off of the study.

We may take your child off the study ARVs if:
- Your child is not able to come to the study visits or we determine that your child cannot meet the study requirements.
- Your child is not able to take the study ARVs.
- The study ARVs are not controlling the HIV in your child’s blood.
• Continuing the study ARVs may be harmful to your child.
• You request to stop the study ARVs for your child.

If your child stops the oral study ARVs early, we will ask you to come back to the clinic with your child about four weeks after your child stops the oral study ARVs (see #14 above). Your child will not have any other visits after this.

If your child stops the ARV shots early, we will ask you to come back to the clinic with your child for four or five additional study visits for long-term follow-up (see #15 above). Your child will not have any other visits after these four or five visits.

We may also take your child off the study early if the study is stopped for any reason.

The study cannot provide other types of ARVs, but we will give information, counseling, and referrals to where your child can get care and treatment needed. We will help make sure your child can get ARVs from outside of the study. If the study stops early, every effort will be made to make certain that there is no interruption in your child’s therapy.

18. Please tell us if your child wants to leave the study.

Your child is free to leave the study at any time for any reason. The care that your child receives at this clinic will not be affected, but it is important for us to know about your decision.

If your child stops the study ARVs, we may ask you to return to the study clinic with your child for additional study visits described in #14 and #17 above. If your child stops the study early, we may ask that your child has one final study visit.

We will answer any questions you or your child may have and give you information on how to contact us in the future, if you wish.

After the study

19. Receiving the study ARVs after the study is over.

As your child comes to the end of the study, we will work with you to plan for your child’s care and treatment outside the study. It is important that we plan for this in advance, so that there is no gap in your child taking ARVs as they finish the study. Taking ARVs without interruption is the best known way for your child to stay healthy.

We will tell you where your child can go to receive needed care and treatment after they finish the study. If your child is gaining benefit from the injection ARVs given in the study, the company that is providing these ARVs (ViiV) will try to provide these injection ARVs to your child. They will be provided until they are otherwise available locally, until your child is no longer gaining benefit, or if the company decides to stop studying the ARVs. However, there is no guarantee this will be possible. If this is not possible, your child will need to switch to other oral ARVs that are available locally. We will explain the options to you and help ensure your child’s access to ARVs outside the study. We will also contact you again within the first four weeks after your child finishes the study to confirm that your child is getting ARVs.
**Risks of the study**

Taking part in this study may involve some risks and discomfort. The risks are different for each phase of the study. Cohort 2-Phase 1 risks include: risks from blood draws, risks from the study pills (CAB and RPV), and risks to your child’s privacy.

Cohort 2-Phase 2 risks include: risks from blood draws, risks from receiving the injection, risks from the study pills (CAB and RPV) and the study shots (long-acting CAB and RPV), risks of switching ARVs and risks to your child’s privacy.

Cohort 2-Phase 3 risks include: risks from blood draws, and risks to your child’s privacy.

20. **Risk from blood draws**

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

21. **Risk from receiving the injection**

People in other studies who have received the CAB LA and RPV LA shots said they had pain, skin irritation, skin redness, bumps, swelling, itching, bruising at the spot where they got the shot. Most reactions go away in a week or less but sometimes they can last a long time. Most people usually do well with them and rarely need to stop the drug.

The shots will be given in the muscles of your child’s buttocks. The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve.

The risks of this are not well understood, but could make drug levels too low or too high. If too low, the drug may not work against your child’s HIV. If RPV is too high, there could be a change in your child’s heart beat, which in severe cases can be life-threatening. Everything possible will be done to decrease this risk, including watching your child for problems during the study. If your child’s doctor thinks that the injection was not given the right way, your child might be asked to stay in the clinic up to 2 hours after the injection to watch how your child is doing and extra tests may be needed to be sure your child is safe. If you or your child are worried about this risk, talk to your child’s doctor.

22. **There are risks from the study ARVs**

All ARVs can cause side effects. This includes the ARVs your child is currently taking and the ARVs that are given in the study. Some side effects are minor; others can be severe. Some side effects are common; others are rare. Some people who take ARVs have some of the side effects. Other people have different side effects, or no side effects.

The most common and most serious side effects of the study ARVs, CAB and RPV, are listed below. This is based on what we know now about CAB and RPV. There may be other side effects that we do not know about now. This may be especially true for adolescents, because this is the first study of CAB and RPV in adolescents.

This form does not list all possible side effects of all ARVs. If your child joins the study, we will tell you more about the ARVs your child will be taking. At each study visit, we will check on whether the ARVs may be causing side effects. We will also tell you what to do if your child has side effects. If you or your child have questions or concerns at any time, please tell us.
23. Some side effects from the CAB pills and the CAB LA

Many people have received CAB pills or the CAB LA shot in other studies. The table below lists side effects from other studies of CAB with people who have HIV. It is not known if CAB, other drugs or the patient’s other health problems caused or affected these. Some of these are the same side effects as RPV (see #24 below).

### Common Side Effects of CAB

<table>
<thead>
<tr>
<th>Very Common Side Effects of CAB</th>
<th>Common Side Effects of CAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea (feeling sick to the stomach)</td>
<td>• Rash</td>
</tr>
<tr>
<td>• Diarrhea or loose stools</td>
<td>• Itching</td>
</tr>
<tr>
<td>• Runny nose, sore throat/Upper respiratory tract infection</td>
<td>• Vomiting (being sick)</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Stomach pain and discomfort</td>
</tr>
<tr>
<td>• Fever</td>
<td>• Problems sleeping</td>
</tr>
<tr>
<td>• Lack of energy</td>
<td>• Abnormal dreams/nightmares</td>
</tr>
<tr>
<td></td>
<td>• Feeling light headed</td>
</tr>
<tr>
<td></td>
<td>• Depression</td>
</tr>
<tr>
<td></td>
<td>• Passing gas or wind</td>
</tr>
<tr>
<td></td>
<td>• Joint or muscle pain</td>
</tr>
<tr>
<td></td>
<td>• Increase in the level of enzymes made in the muscles (creatine phosphokinase)</td>
</tr>
</tbody>
</table>

The following effects have also been seen in some of the people who received CAB pills or the CAB LA shot in other studies:

**Abnormal liver tests:**

A small number of people across all studies (just over 1% of 1644 participants as of April 2017) had abnormal liver tests requiring them to stop CAB. Some abnormal liver tests were explained by other things such as a new virus infection, like Hepatitis A, B or C. Very few people did not have another possible reason so it is possible that a mild form of liver damage happened from taking CAB. The liver tests got better after stopping CAB, showing that any damage was temporary.

Blood tests to check the health of your child’s liver will be done during the study. Your child’s study doctor will tell you if your child needs to stop taking the study drugs or if other action is needed. If your child stops taking the study drug, they may be able to re-start the study drug or they may need to change their usual ARVs.

**Seizures/convulsions:**

Seizures have been seen (rarely) in people with and without HIV. They are not thought to be caused by CAB, but the study staff will ask you about them.

In other studies, two people without HIV had a history of seizures (epilepsy), and had a seizure about 3 months and 9 months after starting CAB. One other person with HIV but without a history of seizures, had seizures about one year after starting CAB. This participant had a long period of seizures without medical treatment and died. It
is not known if CAB was part of the reason for seizures in these people. If your child has a history of seizures, please let your child’s study doctor know.

24. Some side effects from the RPV pills and the RPV LA

The following side effects have been seen with rilpivirine in HIV-infected patients in clinical trials. Oral RPV (Edurant) is a marketed drug and many more people have received Edurant. The side effects of Edurant are more known than the side effects for CAB, and more known than the side effects of RPV LA. Many people have taken part in studies and received RPV LA, and some also received CAB LA. The following side effects have been seen in studies in people with HIV taking RPV.

### Common Side Effects of RPV

<table>
<thead>
<tr>
<th>Very Common Side Effects of RPV</th>
<th>Common Side Effects of RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Problems sleeping</td>
<td>• Rash</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Feeling light headed</td>
<td>• Abnormal dreams</td>
</tr>
<tr>
<td>• Nausea (feeling sick to the stomach)</td>
<td>• Lack of energy</td>
</tr>
<tr>
<td>• Increase in the level of liver enzymes</td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td>• Sleepiness</td>
</tr>
<tr>
<td></td>
<td>• Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>• Stomach pain and discomfort</td>
</tr>
<tr>
<td></td>
<td>• Dry Mouth</td>
</tr>
<tr>
<td></td>
<td>• Sleep problems</td>
</tr>
</tbody>
</table>

The following effects have also been seen in some of the people who received RPV in other studies:

**Abnormal blood tests:**

Other changes in blood tests have also been observed. People with hepatitis B or C or increased in liver tests showing possible liver damage before starting RPV may have worse liver tests while taking RPV. A few cases of liver problems have also been seen in people taking RPV who did not already have any liver problems.

Sometimes allergic reactions can affect body organs, like the liver and cause liver problems which can lead to liver failure. Contact your child’s study doctor right away if your child has any of the following signs or symptoms of liver problems:

- *Yellowing of the skin or whites of the eyes*
- *Dark or tea colored urine*
- *Pale colored stools/bowel movements*
- *Nausea/vomiting*
- *Loss of appetite*
- *Pain, aching or tenderness on the right side below the ribs*
Blood tests to check the health of your child’s liver will be done during the study. Your child’s study doctor will tell you if your child needs to stop taking the study drugs or if other action is needed. If your child stops taking the study drug, they may be able to re-start the study drug or they may need to change their usual ARVs.

**Skin Rash:**

Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most of rashes got better after one week, and the people did not need to stop taking RPV. However, the study ARVs will need to be stopped for some types of moderate rash and all types of severe rash, which can be life-threatening. If this happens to your child, they will need to come for extra study visits to monitor their health. Some people with rash may also have other signs and symptoms of allergic reaction.

If your child has any type of rash or other skin problems during the study you must tell your child’s study doctor right away, and the doctor may tell your child to stop taking CAB and/or RPV.

25. **There may be other possible risks from the study ARVs.**

**The study ARV shots stay in your body for a long time**

The shots your child gets in this study are long acting, meaning they stay in your child’s body for a long time. In most people, the drugs will no longer be in the body one year after an injection, while in some people low levels of CAB and RPV may still be in the body after one year. If your child develops a side effect to the study drug after the shot, there will be no way to remove the drug from your child’s body. If your child gets a shot of CAB or RPV, we will monitor their health for 48 weeks after their last shot. If your child develops a symptom from these drugs while the drugs are still in their body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

While the amount of study drugs in your child’s body decrease slowly over time after they stop getting shots, the study drugs could stop working against your child’s HIV. When stopping long acting HIV drugs, it will be very important to start taking other HIV medications, as your child’s study doctor tells you, so your child’s HIV medications do not stop working against their HIV.

**Risk of switching ARVs**

If your child joined this study, your child will stop taking the ARVs they are currently taking, and start taking ARVs given by the study. The study ARVs could cause side effects that your child would not have from the ARVs you are currently taking. The study ARVs also may not work as well as the ARVs your child is currently taking. For example, the study ARVs may not work as well to control the amount of HIV in your child’s body. We will test your child’s HIV viral load at most study visits to check on this. If your child’s viral load is higher than expected, your child will have repeat testing, and their use of the study ARVs may be stopped (see #13 above).

**Risk of resistance**

By stopping their previous ARVs and switching to the study ARVs, your child could develop resistance. This could happen if the study ARVs don’t work as well to control the amount of HIV in your child’s body. Resistance means that the ARVs may not work against HIV if these ARVs are taken again in the future. To stop resistance, it is important that your child takes the ARVs as instructed, and does not miss any doses.
Mental Illness

Some people with HIV sometimes have feelings of depression or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with drugs called integrase inhibitors [INIs] for HIV like CAB, have had suicidal thoughts and actions, particularly patients with a prior history of depression or mental health illness.

Tell the study doctor if your child has a history of mental health illness. If your child has thoughts of hurting or killing their self or have any other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

Possible effects on pregnancy or unborn babies

HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if CAB or RPV are safe in pregnancy.

There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug.

Early results from one large study in Botswana showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects of the brain or spine in the new baby. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.

CAB is not the same drug as DTG. We do know that CAB and DTG belong to the same class of medications and work in a similar way to treat HIV infection. We do not know if CAB can cause brain or spine defects in babies.

Girls who are able to become pregnant must agree to use certain effective methods of birth control to be in this study (see #5 above). If your child becomes pregnant during the study, please let us know right away.

Immune reconstitution syndrome

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases may occur soon after starting combination ARVs but can also occur later. Some of these symptoms may be life threatening. If your child starts having new symptoms, or if you notice that any of your child’s existing symptoms are getting worse after starting the ARVs, tell your child’s doctor immediately.

Abnormal placement of body fat and wasting

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
26. There could be risks of disclosure of your child’s information.

We will make every effort to keep your child’s information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your child’s name will be written on some records.

Despite our best efforts to keep your child’s information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly. Your child could feel stress or embarrassment.

To help us protect your child’s privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify your child, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify your child. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your child’s participation in the study to others, if you wish.

Benefits of the study

27. There may be a direct benefit to your child from being in the study.

By joining the study, your child will be part of the search for ARVs that may be better for adolescents. We do not know if being in the study will benefit your child in any way. There may be a direct benefit to your child by taking part in this study, but no guarantee can be made. For example, if your child gets shots of CAB and RPV, they might prefer having monthly shots instead of taking daily pills. The study ARVs may have fewer side effects than the previous ARVs your child was taking. The study drugs may also lower the amount of HIV in the blood. There may also be a benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. It is also possible that your child may receive no direct benefit from this study. Information learned from this study may help other adolescents with HIV.

Your child will have regular visits here and frequent checks on your child’s health, including tests for amount of HIV in your child’s blood, called viral load. It is possible that the study ARVs will slow your child’s HIV infection. Information learned from this study may help other adolescents with HIV.

Other information about the study

28. There are no costs from being in the study.

There are no costs to you for study visits, CAB, RPV or procedures.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).]
29. **Study records may be reviewed by study staff and groups that oversee the study.**

Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child’s name or identify your child personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

Your child’s study information may be given to other authorities if required by law. [Sites add more specific detail here as needed; example follows:] For example, we are required to report any significant risk of harm to your child or others.

30. **If your child gets sick or injured, contact us immediately.**

Your child’s health is important to us. We will make every effort to protect your child’s well-being and minimize risks. It is possible, however, that your child could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat your child or tell you were your child can get treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through [site name or] the U.S. National Institutes of Health.

**Whom to contact**

31. **If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:  
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your child’s rights as research participants or concerns about how your child is being treated in the study:  
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]
• If your child has any health or other problems that may be related to study participation:
  [insert name and telephone number of investigator or other study staff]

• If you want your child to leave the study:
  [insert name and telephone number of investigator or other study staff]

**Signatures**

**If you agree to allow your child to participate in this study, please sign or make your mark below.**

Before deciding whether to allow your child to participate in this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of your child if you decide to allow your child to join.

If you decide to allow your child to join, we will tell you any new information from this study or other studies that may affect your child’s health, welfare, or willingness to stay in the study. You are welcome to ask questions or request more information at any time. If you want the results from this study, please tell the study staff.

You do not give up any rights by signing this form.

[Insert signature blocks as required by site IRB/EC policies.]

Name of Participant (print)

__________________________________________  __________________________  __________
Name of Parent/Guardian/ Legally Authorized Representative  Signature of Parent/Guardian Legally Authorized Representative  Date
Legally Authorized Representative (print)

__________________________________________  __________________________  __________
Name of Study Staff Conducting Consent Process Name (print)  Signature of Study Staff  Date

__________________________________________  __________________________  __________
Name of Witness (as appropriate; print)  Signature of Witness  Date
Appendix II-C: Sample Parental Informed Consent Form for Specimen Storage and Future Use for parents/guardians of adolescents who cannot provide independent informed consent for study participation

IMPAACT 2017

Version 2.0, dated 16 August 2018

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

You have decided to allow your child to join the study named above. As part of the study, your child will have blood and urine collected. After these samples are tested for the study, some samples may be left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

This form gives information about use of extra samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

1. It is your decision whether or not to allow the extra samples to be used.

You are free to say yes or no, and to change your mind at any time. Your decision will not affect your child’s participation in the study. If you say no, all extra samples will be destroyed.

2. If you agree, your child’s extra samples will be kept in a repository.

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. If you agree to have extra samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept [sites may insert time limits or additional site-specific requirements here if required by local authorities].

3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, the extra samples could also be used for research that looks at your child’s genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people’s genes can help explain why some people get a disease while others do not. Your child’s samples would only be used to look at genes related to HIV and the immune system.

Any research done with the extra samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.
The research done with extra samples is not expected to give any information relevant to your child’s health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your child’s study records.

4. **There is little risk to your child.**

When extra samples are used for research, they are labeled with a code number only. To protect your child’s privacy, no names are used. However, information such as age, gender, HIV status, and other health information may be linked to the samples. Information on the ARVs your child received in the study may also be linked to the samples.

There may be some risks from tests of your child’s genes. If others found out the results of these tests, they could treat your child badly or unfairly. However, this is almost impossible because the results will not be given to the study staff, or to you, or to your child and will not be in your child’s study records.

5. **There may be no benefit to your child.**

By allowing extra samples to be used for research, your child will be part of the search for new information that may benefit people with HIV in the future. However, the research done with the extra samples is not expected to directly benefit your child in any way.

6. **You will not be paid for use of your child’s samples.**

There is no cost to you for use of your child’s extra samples. The samples will not be sold, and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with your or your child.

7. **Information from research using extra samples may be reviewed by groups that oversee the research.**

These groups include:
- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research
- Other local, US, or international regulatory entities

The people who do research with the extra samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with the extra samples may be presented publicly or published. However, no presentation or publication will use your child’s name or identify your child personally.

8. **If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about use of your child’s extra samples:
  [insert name and telephone number of investigator or other study staff].

- If you later change your mind about use of your child’s extra samples:
  [insert name and telephone number of investigator or other study staff].
• If you have questions about your child’s rights as a research participant or concerns about how your child is being treated in the study:

[insert name and telephone number of IRB/EC contact person or other appropriate person/organization].

Signatures

Before deciding whether to allow your child’s extra samples to be used for research, make sure you have read this form, or had it read to you. Make sure all of your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination if the level of risk to children in the categories specified in 45 CFR 46.404-407. Separate consent decisions must be documented for genetic testing].

For YOUR CHILD’s extra samples, write your initials or make your mark next to your choice.

__________  I allow my child’s extra samples to be used for research on HIV, the immune system, ARVs, and other diseases. I also allow my child’s samples to be used for tests of his or her genes.

__________  I allow my child’s extra samples to be used for research on HIV, the immune system, ARVs, and other diseases. I do not allow my child’s samples to be used for tests of his or her genes.

__________  I do not allow my child’s extra samples to be used for any research.

[Insert signature blocks as required by site IRB/EC policies.]

Name of Participant (print)

Name of Parent/Guardian/ Legally Authorized Representative (print)  Signature of Parent/Guardian Legally Authorized Representative Date

Name of Study Staff Conducting Consent Process Name (print)  Signature of Study Staff Date

Name of Witness (as appropriate; print)  Signature of Witness Date
Appendix III: Sample Informed Consent Forms

Appendix III-A: Sample Informed Consent Form for Participation in Cohort 1
for adolescents who can provide independent informed consent for study participation

IMPAACT 2017

Version 2.0, dated 16 August 2018

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

You are being asked to take part in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide to participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the study

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and [insert site name]. The person in charge of the study at [insert site name] is [insert name of IoR].

The study is being done to test two anti-HIV medicines (antiretrovirals or ARVs) in adolescents 12 to less than 18 years old who have HIV. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV). HIV is the virus that causes AIDS.

The study will include up to 155 adolescents from the United States. There will be two groups of adolescents, called Cohort 1 and Cohort 2. This form is about Cohort 1. Participants in Cohort 1 will be in the study for at least 16 weeks (4 months) and then up to an additional 48 weeks (12 months) as part of long-term follow-up, for a total of 64 weeks (16 months).

The United States National Institutes of Health and the company that makes CAB and RPV, ViiV Healthcare, are paying for this study.

1. The study is testing CAB and RPV in adolescents.

People with HIV usually take a combination of ARVs daily to stay healthy. There are not as many ARVs available for adolescents as for adults because many ARVs have not yet been tested in adolescents. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV when taken as pills and when given as shots in adolescents. The pills are taken every day. The shots are given every 4
weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer to have the shots rather than taking pills.

RPV pills (25mg taken once daily) have been shown to be safe and effective for both adults and adolescents 12 years and older with HIV. These pills are already approved by the US Food and Drug Administration (FDA) for adults and adolescents with HIV.

RPV shots (600mg), CAB pills (30mg), and CAB shots (400mg) are now being tested in adults with HIV. This will be the first study of these ARVs in adolescents. So far, the testing in adults has shown that RPV shots, CAB pills, and CAB shots work as well as other ARVs that are approved. However, because these ARVs are still being tested, there may be some effects that we do not know about yet.

This study will test the effects of these ARVs in adolescents. The study will look at whether these ARVs:
- Are being given at the correct dose for adolescents
- Are safe and well-tolerated
- Can control HIV in adolescents as well as other ARVs

The study will also look at how willing adolescents are to take these ARVs.

Cohort 1 of this study will be done first to test CAB and RPV pills when taken for about 1 month followed by CAB and RPV shots when taken for about 2 months. Adolescents in Cohort 1 will take either CAB pills followed by CAB shots or RPV pills followed by RPV shots. They will keep taking their usual ARVs (see #8 below for more information). If the results from Cohort 1 show that CAB pills, CAB shots and RPV shots are safe and that the dose is correct, Cohort 2 will start. Cohort 2 will test whether CAB and RPV pills taken together, followed by CAB and RPV shots taken together are safe and can control HIV when adolescents stop taking their previous ARVs. Some adolescents from Cohort 1 may be eligible to also take part in Cohort 2. More information about the study and CAB and RPV is given in the rest of this form.

2. **Only adolescents who are eligible can participate in the study.**

If you decide to join the study, we will first do some tests to find out if you are eligible. More information about the tests is given in #4 (see below). If you are eligible, you will be entered in the study. If you are not eligible, you cannot be entered in the study.

3. **It is your decision whether or not you join the study.**

Deciding to join the study is voluntary (your choice). You may choose to join or not join. If you choose to join, you can change your mind and leave the study. Your choices will have no effect on the medical care you would normally receive. Your access to services, and the benefits and rights you normally have, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

No matter what you decide about the study, it is important for you to keeping taking ARVs. **This is the best known way for you to stay healthy.**
Finding out if you are eligible

4. We will ask questions, examine you, and discuss the study requirements with you.

To find out if you are eligible for the study, we will:

- Review your medical records.
- Ask questions about you, your health, and the medications you take.
- Talk with you about birth control (ways to prevent pregnancy).
- Talk with you about the study requirements and if you are able to meet these requirements.
- Do a physical exam. This will include looking at your genitals to see your stage of development. For girls, this will also include looking at your breasts.
- Do an electrocardiogram (ECG). This is to test how well your heart is working.
- Draw between 17-23mL (about 3-5 teaspoons) of blood for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Confirm that you have HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
  - Check the amount of HIV in your blood. This is called your HIV viral load.
  - Some blood will be saved for later testing for resistance to ARVs. This test shows whether different ARVs may work against the HIV in your blood.

These procedures will take about 4 hours [here and throughout this form, sites may modify the expected visit duration as needed].

5. For girls, we will also test for pregnancy.

Girls in this study cannot be pregnant. Girls should not join this study if they are pregnant or intend to become pregnant within 30 days after stopping the study ARV pills or within 48 weeks after stopping the study shots. Because the effects of the study ARVs on unborn babies are unknown, you should not become pregnant while in this study. For all girls in the study, we will collect urine or blood to test for pregnancy.

There are certain effective methods of birth control that girls who are able to become pregnant must use while in this study. These effective methods must be continued for 30 days after stopping the study ARV pills, or for at least 48 weeks after stopping the study ARV shots. Girls who are able to become pregnant, must agree to use these methods in order to take part in the study. We will help make sure you can get effective methods by providing them here in the clinic or offering a referral. At study visits when you will receive study medicines (either the pill or shot), we will need to confirm that you are using effective birth control before giving you the study medicines.

Girls who become pregnant during the study will stop taking the study medicines and enter the long-term safety follow-up phase of the study (see #16 below). We will contact you to find out the outcome of the pregnancy even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. You must give us permission before we can share these results with your parents/guardians. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.]
If you are pregnant, your doctor may report your pregnancy to the Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry assists patients and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about you, such as your name, initials, contact information, or date of birth.

6. **We will tell you if you are eligible.**

We will give you the results of all procedures and explain the results to you. We will tell you about getting care, treatment and any other services you may need. While waiting for the results, it is important for you to keep taking your usual ARVs.

If you are not eligible for the study for any reason, we will tell you this. You will not be entered in the study. You can and should continue to receive medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services you may need.

If you do not enter the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If you are eligible for the study, you will be entered into the study.

**Entering the study**

7. **If you are eligible, you will enter the study.**

On the day you enter the study we will:

- Review your medical records.
- Talk with you about your ARV use
- Talk with you about preventing pregnancy
- Ask you questions about what you think about CAB or RPV
- Do a physical exam.
- Draw between 20mL (about 4 teaspoons) of blood for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Check how much the virus has affected your ability to fight the virus. This is called CD4 cell count.
  - The tests will check your HIV viral load. Some blood will also be saved for later resistance testing.
- For girls, we will collect urine or blood for a pregnancy test.

At the study entry visit we may also do an ECG to look at your heart. This will only be needed if you enter the study more than 2 weeks after your first visit.

At this visit, you will start taking CAB or RPV pills. We will give you the pills and explain how to take them. You will take your first dose at the visit. You will continue taking your usual ARVs.

This visit will take about 4 hours.

**Being in the study**

8. **After entering the study, participants take CAB or RPV pills for 4-6 weeks and then switch to CAB or RPV shots.**
For participants in Cohort 1, there are three phases of the study. All participants will take part in Cohort 1-Phase 1. Only those who are eligible will take part in Cohort 1-Phase 2. Participants who take part in Cohort 1-Phase 2 will also take part in Cohort 1-Phase 3, called the long-term follow-up safety phase.

In Cohort 1-Phase 1, you will keep taking your usual ARVs. You will also take either CAB or RPV pills. Whether you take CAB or RPV will be based on the type of usual ARVs you take. The pills must be swallowed whole. They cannot be broken or crushed. They should be taken with food. This phase lasts for about 4-6 weeks. You will have 3 visits during this time. At these visits, we will check on how you are doing while taking the pills (see #9 for more information). We will also check on whether you are eligible for Cohort 1-Phase 2.

If you are eligible for Cohort 1-Phase 2, you will keep taking your usual ARVs. You will stop taking the CAB or RPV pills and start getting either CAB or RPV shots. The ARV you get in the shot will be the same ARV you were taking by pill. The shots are long-acting, meaning the medicine stays in the body for a long time. This phase lasts about 12 weeks. You will have 8 visits during this time and you will get shots at three of these visits. Each shot is about 3mL (about 1 teaspoon). The shots are given in the buttocks (bottom “cheeks”). At each of these three visits, you will be given one shot of CAB or one shot of RPV. At all of the Phase 2 visits, we will check on how you are doing while getting the shots (see #11 for more information).

After Cohort 1-Phase 2, you will then take part in the long-term follow-up safety phase of the study. This phase lasts about 48 weeks. You child will keep taking your usual ARVs. There will be 4 or 5 visits during long-term follow up (see #16 for more information).

9. In Cohort 1-Phase 1, you will have 2 visits.

Visits in this phase will be scheduled 2 weeks apart. [Sites to modify] Each visit will take about 1-3 hours. At each of these visits, we will:

- Review your medical records.
- Talk with you about your ARV use
- Do a physical exam.
- For girls, we will also collect urine or blood to test for pregnancy.
- Talk with you about preventing pregnancy.
- Remind you to bring the oral CAB or oral RPV to the study clinic.

At two of these visits (Week 2 and Week 4a), we will draw about 5mL (about 1 teaspoon) of blood for tests. These tests will check your blood cells and how well your liver and kidneys are working.

At the second visit (Week 2), we will also draw about 12mL (about 2-3 teaspoons) blood for tests. This test will check your HIV viral load. Some blood will be saved for later resistance testing.

At the second visit (Week 2), we will also do an intensive pharmacokinetic (PK) test. This is a test to look at the amount of CAB or RPV in your blood. At this visit, we will ask you when you took CAB or RPV in the past three days. [Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection.] For three days before this visit, you must be sure to take CAB or RPV on time and in the morning. This is very important. We will help you remember this before the visit.

If you are taking oral CAB, we will need to draw your blood seven times during the visit, before and after taking CAB. We will also remind you not to take CAB before coming to this visit. When you come to the visit, we will draw your blood, then you will take CAB, and then we will draw your blood 6 more times, about 1, 2, 3, 4, 8 and 24 hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 14mL (about 3 teaspoons).
If you are taking oral RPV, we will need to draw your blood four times during the visit, before and after taking RPV. We will remind you not to take RPV before coming to this visit. When you come to the visit, we will draw your blood, then you will take RPV, and then we will draw your blood 3 more times, about 4, 8 and 24 hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 8mL (about 2 teaspoons).

[Sites: modify language as appropriate to indicate procedures for the intensive PK collection. For the intensive PK tests, a small plastic tube will be placed in your arm to draw blood samples. This tube is attached to a plastic needle so that we can draw blood several times. We will not need to stick you with a needle each time. The plastic tube may stay in place for the blood draws in the first 24 hours.]

[Sites: modify language as appropriate to indicate procedures for intensive PK visit and overnight stays – You may need to stay at the clinic or hospital for up to 24 hours. If the study clinic is able, you may be allowed to stay at the clinic the night before and during your first PK visit.]

10. We will tell you if you are eligible for Cohort 1-Phase 2.

At the Week 4b visit, we will determine if you are eligible for Cohort 1-Phase 2. At this visit, we will:
- Review your medical records.
- Talk with you about your ARV use.
- Do a physical exam.
- Ask you questions about what you think about CAB or RPV.
- Talk with you about preventing pregnancy.
- Draw about 12mL (about 2-3 teaspoons) blood for tests. These tests will check your HIV viral load. Some blood will be saved for later resistance testing.
- For girls, we will also collect urine or blood to test for pregnancy.
- Remind you to bring the oral CAB or oral RPV to the study clinic.
- [Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection. Remind you to take your oral CAB or oral RPV in the morning for the three days before this visit.]

If you are not eligible, you will stop taking oral CAB or oral RPV and will complete a final study visit about 4 weeks after your last oral dose (see #15 for more information).

If you are eligible for Cohort 1-Phase 2, you will continue taking your usual ARVs. You will take your last dose of oral CAB or oral RPV at the Week 4b visit. We will also give you the first shot of CAB or the first shot of RPV at the Week 4b visit. We will remind you not to take oral CAB or oral RPV before coming to this visit. You will take oral CAB or oral RPV at the study clinic before the first shot of CAB or the first shot of RPV.

At this visit, we will also look closely at the amount of CAB or RPV in your blood. To do this, we will need to draw your blood two times during the visit, before taking oral CAB or RPV and after getting a shot of CAB or RPV. When you come to the visit, we will draw your blood, then you will take your oral CAB or RPV and get a shot of CAB or RPV, and then we will draw your blood again, about two hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 4mL (less than 1 teaspoon).

11. In Cohort 1-Phase 2, you will have 8 visits (Weeks b-16).

The first visit in Cohort 1-Phase 2 will be the Week 4b visit, which is described in #10 above. The other visits in this phase will be scheduled 1-3 weeks apart. [Sites to modify] Each visit will take about 1-3 hours.
At each of these visits, we will:

- Review your medical records.
- Talk with you about preventing pregnancy.
- Do a physical exam. At the Week 16 visit, this will include looking at your genitals to see your stage of development. For girls, this will also include looking at your breasts.

At each of these visits we will look at the amount of CAB or RPV in your blood. At 6 of these visits (Week 5, 6, 8, 13, 14, 16), we will draw about 2mL of blood (less than 1 teaspoon) to do this. At the Week 12 visit, we will look very closely at the amount of CAB or RPV in your blood. To do this, we will need to draw your blood two times during the visit, before and after getting a shot of CAB or RPV. When you come to the visit, we will draw your blood, then you will get a shot of CAB or RPV, and then we will draw your blood again, about two hours later. Each time we will draw 2mL (less than 1 teaspoon), for a total of 4mL of blood (less than 1 teaspoon).

At 5 of these visits (Weeks 5, 8, 12, 13 and 16) we will also draw about 5mL of blood (about 1 teaspoon) for tests. These tests will check your blood cells and how well your liver and kidneys are working.

At 3 of these visits (Weeks 8, 12 and 16) we will also draw about 12mL of blood (about 2-3 teaspoons) for other tests. These tests will check your HIV viral load. Some blood will be saved for later resistance testing. We will ask your child questions about getting shots of CAB or RPV.

At 1 of these visits (Week 16), we will also draw about 8mL of blood (between 1 and 2 teaspoons) for tests. These tests will check your child’s blood cells and CD4 count.

At 2 of these visits (Weeks 13 and 16) we will also do an ECG to look at your heart.

At 2 of these visits (Weeks 8 and 12) we will also give you a shot of either CAB or RPV.

At 2 of these visits (Weeks 8 and 16) we will also talk with you about your ARV use.

For girls, at 3 of these visits (Weeks 8, 12 and 16) we will also collect urine or blood to test for pregnancy.

Up to two weeks after the Week 8 visit, we will contact you by phone (call or text you) to see how you are doing after the shot of CAB or RPV. You can also contact us if you have any questions or concerns. If you have any side effects, we will give you advice on how to manage them. We may also ask you to come back to the clinic so we can see you in person. See #22 and 23 (below) for more information about side effects.

12. In-depth phone interview

We are very interested to understand what adolescents think about getting their ARV’s as shots. You will be asked if you would like to complete an in-depth phone interview. If you would like to take part in the interview, then you may be contacted to have the interview after getting the first shot of CAB or RPV.

If contacted, this interview will take approximately 1-2 hours, and will ask about how you feel about having shots of CAB or RPV. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about them receiving the shots. The interview may take place at or in between the Week 4b, 5, 6, 8, and 12 study visits, or during the long-term follow-up safety phase. The interview will only take place once. The interview will be audio recorded and written down in a report. Your name will not be included in the report. Not all participants will be contacted for the interview. You do not have to do the interview to take part in this study.
We may also ask your parent or caregiver to complete an in-depth interview. This interview would ask them how they felt about you having shots of CAB or RPV.

13. We will tell you if you are eligible for Cohort 2.

After your last visit in Cohort 1-Phase 2, we will tell you if are eligible for Cohort 2 or if you need additional tests to see if you qualify for Cohort 2.

If you are not eligible for Cohort 2, or if Cohort 2 is not ready, you will stop getting shots of CAB or RPV and will enter Cohort 1-Phase 3, also called the long-term follow-up safety phase (see #16 for more information). We will let you know when Cohort 2 is ready and if you need additional tests to see if you qualify for Cohort 2.

If you are eligible for Cohort 2 and when Cohort 2 is ready, you can enter into Cohort 2.

14. Adolescents may have an extra visit if their HIV is not controlled.

Participants will have viral load tests at almost all visits to check the amount of HIV in the blood. If tests show that the viral load is higher than expected (above 200 copies/mL) you will have repeat testing. This may occur as part of another study visit or may occur as an extra study visit.

The extra visit will take about 1-2 hours. At this visit we will:
- Review your medical records.
- Do a physical exam.
- Draw about 14mL (about 3 teaspoons) of blood for tests. The tests will:
  - Check your HIV viral load.
  - Check the amount of CAB or RPV in the blood.
  - We will save some blood for later resistance testing.
- Talk with you about preventing pregnancy.
- For girls, we will also collect urine or blood to check for pregnancy.

If the repeat test also shows an increased amount of HIV in your blood, you will stop taking the study product. If you were getting shots of CAB or RPV, you will enter long-term follow-up (more information in #16 below).

15. If you are not eligible to receive shots of CAB or RPV you will stop the study early.

If you are not eligible to get shots of CAB or RPV in Cohort 1, you will stop taking oral CAB or oral RPV and will complete a final study visit about 4 weeks after your last oral dose.

During this visit, we will:
- Review your medical records.
- Do a physical exam. This will include looking at your genitals to see the stage of development. For girls, this will also include looking at the breasts.
- Draw blood for tests. This would be about 17mL of blood (about 3-4 teaspoons) for these tests. These tests will check:
  - Your blood cells.
  - How well your liver and kidneys are working.
  - Your HIV viral load.
  - Some blood will be saved for future resistance testing.
• Talk with you about preventing pregnancy.
• For girls, we will also collect urine or blood to check for pregnancy.
• Ask you questions about taking CAB or RPV.
• We will also talk with you about your ARV use.

16. If you are not eligible to enroll in Cohort 2, or if Cohort 2 is not yet open, you will enter Cohort 1-Phase 3, also called the long-term follow-up safety phase.

If you are not able to enroll in Cohort 2 after getting shots in Cohort 1-Phase 2, or if Cohort 2 is not yet open, you will enter a long-term follow-up safety phase after the last shot of study product. At this time, you will stop getting shots of CAB or RPV. For females, if you become pregnant, you will enter this phase of the study after your last dose of study medicine, whether the pill or the shot. You will keep taking your usual ARVs. There will be 4 or 5 additional visits during the long-term follow-up.

These visits will be scheduled 4, 12, 24, 36 and 48 weeks after your last shot of CAB or RPV. Each of these visits will take about 1-3 hours. At these visits, we will:
• Review your medical records.
• Do a physical exam. At the final long-term follow-up visit, this will include examination of your genitals to see the stage of development. For girls, this will also include looking at your breasts.
• Talk with you about preventing pregnancy.
• Draw blood for tests. This would be about 19mL of blood (about 4 teaspoons) for these tests. These tests will check:
  o Your blood cells.
  o How well your liver and kidneys are working.
  o Your HIV viral load.
  o The amount of CAB or RPV in the blood.
  o Some blood will also be saved for future resistance testing.
• For girls, we will also collect urine or blood to check for pregnancy.
• At two of these visits (4 weeks and 48 weeks after your last shot of CAB or RPV) we will talk with you about your ARV use.
• At the final visit (48 weeks after your last shot of CAB or RPV), we will also ask you questions about getting shots of CAB or RPV.

For participants who complete the Week 16 visit in Cohort 1-Phase 2, the first long-term follow-up visit will be skipped entirely. The Week 16 visit and the first long-term follow-up visit are very similar and do not need to be conducted twice.

17. The tests for the amount of CAB or RPV in your blood will be done at different laboratories.

We will do most of the tests of blood or urine here at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

We will also draw blood to check the amount of CAB or RPV in your blood. This is called a pharmacokinetic (PK) test. The test will be done at other laboratories in the United States or in Ireland. We will not usually give you the results of this test during the study.

18. We may take you off of the study.

We may take you off the study ARVs if:
• You are not able to come to the study visits or we determine that you cannot meet the study requirements.
• You are not able to take the study ARVs.
• The study ARVs are not controlling the HIV in your blood.
• Continuing the study ARVs may be harmful to you.
• You request to stop the study ARVs.

If you stop the oral study ARVs early, we will ask you to come back to the clinic about four weeks after you stop the oral study ARVs (see #15 above). You will not have any other visits after this.

If you stop the ARV shots early, we will ask you to come back to the clinic for four to five additional study visits for long-term follow-up (see #16 above). You will not have any other visits after these four or five visits.

We may also take you off the study early if the study is stopped for any reason.

The study cannot provide other types of ARVs, but we will give information, counseling, and referrals to where you can get care and treatment needed. We will help make sure you can get ARVs from outside of the study. If the study stops early, every effort will be made to make certain that there is no interruption in your therapy.

19. Please tell us if you want to leave the study.

You are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

If you stop the study ARVs, we may ask you to return to the study clinic for additional study visits described in #15 and #16 above. If you stop the study early, we may ask that you have one final study visit.

We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

*Risks of the study*

Taking part in this study may involve some risks and discomfort. The risks are different for each phase of the study. Cohort 1-Phase 1 risks include: risks from blood draws, risk from the study pills (CAB or RPV), and risks to your privacy.

Cohort 1-Phase 2 risks include: risks from blood draws, risks from receiving the injection, risks from the study pills (CAB or RPV) and the study shots (long-acting CAB or RPV) and risks to your privacy.

Cohort 1-Phase 3 risks include: risks from blood draws, and risks to your privacy.

20. Risk from blood draws

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

21. Risk from receiving the injection
People in other studies who have received the CAB LA and RPV LA shots said they had pain, skin irritation, skin redness, bumps, swelling, itching, bruising at the spot where they got the shot. Most reactions go away in a week or less but sometimes they can last a long time. Most people usually do well with them and rarely need to stop the drug.

The shots will be given in the muscles of your buttocks. The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve.

The risks of this are not well understood, but could make drug levels too low or too high. If too low the drug may not work against your HIV. If RPV is too high, there could be a change in your heart beat, which in severe cases can be life-threatening. Everything possible will be done to decrease this risk, including watching you for problems during the study. If your doctor thinks that the injection was not given the right way, you might be asked to stay in the clinic up to [sites to modify] 2 hours after the injection to watch how you are doing and extra tests may be needed to be sure you are safe. If you are worried about this risk, talk to your doctor.

22. There are risks from the study ARVs

All ARVs can cause side effects. This includes the ARVs you are currently taking and the ARVs that are given in the study. Some side effects are minor; others can be severe. Some side effects are common; others are rare. Some people who take ARVs have some of the side effects. Other people have different side effects, or no side effects.

The most common and most serious side effects of the study ARVs, CAB and RPV, are listed below. This is based on what we know now about CAB and RPV. There may be other side effects that we do not know about now. This may be especially true for adolescents, because this is the first study of CAB and RPV in adolescents.

This form does not list all possible side effects of all ARVs. If you join the study, we will tell you more about the ARVs you will be taking. At each study visit, we will check on whether the ARVs may be causing side effects. We will also tell you what to do if you have side effects. If you have questions or concerns at any time, please tell us.

23. Some side effects from the CAB pills and the CAB LA

Many people have received CAB pills or the CAB LA shot in other studies. The table below lists side effects from other studies of CAB with people who have HIV. It is not known if CAB, other drugs or the patient’s other health problems caused or affected these. Some of these are the same side effects as RPV (see #24 below).

### Common Side Effects of CAB

<table>
<thead>
<tr>
<th>Very Common Side Effects of CAB</th>
<th>Common Side Effects of CAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea (feeling sick to the stomach)</td>
<td>• Rash</td>
</tr>
<tr>
<td>• Diarrhea or loose stools</td>
<td>• Itching</td>
</tr>
<tr>
<td>• Runny nose, sore throat/Upper respiratory tract infection</td>
<td>• Vomiting (being sick)</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Stomach pain and discomfort</td>
</tr>
<tr>
<td>• Fever</td>
<td>• Problems sleeping</td>
</tr>
<tr>
<td>• Lack of energy</td>
<td>• Abnormal dreams/nightmares</td>
</tr>
</tbody>
</table>
The following effects have also been seen in some of the people who received CAB pills or the CAB LA shot in other studies:

Abnormal liver tests:

A small number of people across all studies (just over 1% of 1644 participants as of April 2017) had abnormal liver tests requiring them to stop CAB. Some abnormal liver tests were explained by other things such as a new virus infection, like Hepatitis A, B or C. Very few people did not have another possible reason so it is possible that a mild form of liver damage happened from taking CAB. The liver tests got better after stopping CAB, showing that any damage was temporary.

Blood tests to check the health of your liver will be done during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other action is needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual ARVs.

Seizures/convulsions:

Seizures have been seen (rarely) in people with and without HIV. They are not thought to be caused by CAB, but the study staff will ask you about them.

In other studies, two people without HIV had a history of seizures (epilepsy), and had a seizure about 3 months and 9 months after starting CAB. One other person with HIV but without a history of seizures, had seizures about one year after starting CAB. This participant had a long period of seizures without medical treatment and died. It is not known if CAB was part of the reason for seizures in these people. If you have a history of seizures, please let your study doctor know.

24. Some side effects from the RPV pills and the RPV LA

The following side effects have been seen with rilpivirine in HIV-infected patients in clinical trials. Oral RPV (Edurant) is a marketed drug and many more people have received Edurant. The side effects of Edurant are more known than the side effects for CAB, and more known than the side effects of RPV LA. Many people have taken part in studies and received RPV LA, and some also received CAB LA. The following side effects have been seen in studies in people with HIV taking RPV.
Common Side Effects of RPV

<table>
<thead>
<tr>
<th>Very Common Side Effects of RPV</th>
<th>Common Side Effects of RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Problems sleeping</td>
<td>• Rash</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Feeling light headed</td>
<td>• Abnormal dreams</td>
</tr>
<tr>
<td>• Nausea (feeling sick to the stomach)</td>
<td>• Lack of energy</td>
</tr>
<tr>
<td>• Increase in the level of liver enzymes</td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td>• Sleepiness</td>
</tr>
<tr>
<td></td>
<td>• Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>• Stomach pain and discomfort</td>
</tr>
<tr>
<td></td>
<td>• Dry Mouth</td>
</tr>
<tr>
<td></td>
<td>• Sleep problems</td>
</tr>
</tbody>
</table>

The following effects have also been seen in some of the people who received RPV in other studies:

Abnormal blood tests:

Other changes in blood tests have also been observed. People with hepatitis B or C or increased in liver tests showing possible liver damage before starting RPV may have worse liver tests while taking RPV. A few cases of liver problems have also been seen in people taking RPV who did not already have any liver problems.

Sometimes allergic reactions can affect body organs, like the liver and cause liver problems which can lead to liver failure. Contact your study doctor right away if you have any of the following signs or symptoms of liver problems:

- *Yellowing of the skin or whites of the eyes*
- *Dark or tea colored urine*
- *Pale colored stools/bowel movements*
- *Nausea/vomiting*
- *Loss of appetite*
- *Pain, aching or tenderness on the right side below the ribs*

Blood tests to check the health of your liver will be done during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other action is needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual ARVs.

Skin Rash:

Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most of rashes got better after one week, and the people did not need to stop taking RPV. However, the study ARVs will need to be stopped for some types of moderate rash and all types of severe rash, which can be life-threatening. If this happens to you, you will need to come for extra study visits to monitor your health. Some people with rash may also have other signs and symptoms of allergic reaction.
If you have any type of rash or other skin problems during the study you must tell your study doctor right away, and the doctor may tell you to stop taking CAB and/or RPV.

25. **There may be other possible risks from the study ARVs.**

_The study ARV shots stay in your body for a long time_

The shots you get in this study are long acting, meaning they stay in your body for a long time. In most people the drugs will no longer be in the body one year after an injection, while in some people low levels of CAB and RPV may still be in the body after one year. If you develop a side effect to the study drug after the shot, there will be no way to remove the drug from your body. If you get a shot of CAB or RPV, we will monitor your health for 48 weeks after your last shot. If you develop a symptom from these drugs while the drugs are still in your body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

While the amount of study drugs in your body decrease slowly over time after you stop getting shots, the study drugs could stop working against your HIV. When stopping long acting HIV drugs, it will be very important to start taking other HIV medications, as your study doctor tells you, so your HIV medications do not stop working against your HIV.

_Risk of resistance_

All ARVs can cause some resistance if not taken correctly. Resistance means that the ARVs may not work against HIV if these ARVs are taken again in the future. To stop resistance, it is important that you take the ARVs as instructed, and does not miss any doses.

_Effects on other ARVs_

We do not expect the study ARVs to change the way other ARVs work in the body. For example, if you were to join the study, we would expect the ARVs you are currently taking to keep working to control the amount of HIV in your body. We also do not expect the study ARVs to cause more or worse side effects from other ARVs. However, this study is being done to learn more about these kinds of possible effects.

_Mental Illness_

Some people with HIV sometimes have feelings of depression or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with drugs called integrase inhibitors [INIs] for HIV like CAB, have had suicidal thoughts and actions, particularly patients with a prior history of depression or mental health illness.

Tell the study doctor if you have a history of mental health illness. If you have thoughts of hurting or killing yourself or have any other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

_Possible effects on pregnancy or unborn babies_

HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if CAB or RPV are safe in pregnancy.
There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug.

Early results from one large study in Botswana showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects of the brain or spine in the new baby. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.

CAB is not the same drug as DTG. We do know that CAB and DTG belong to the same class of medications and work in a similar way to treat HIV infection. We do not know if CAB can cause brain or spine defects in babies.

Girls who are able to become pregnant must agree to use certain effective methods of birth control to be in this study (see #5 above). If you become pregnant during the study, please let us know right away.

**Immune reconstitution syndrome**

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases may occur soon after starting combination ARVs but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or if you notice that any existing symptoms are getting worse after starting the ARVs, tell your doctor immediately.

**Abnormal placement of body fat and wasting**

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:
- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

**26. There could be risks of disclosure of your information.**

We will make every effort to keep your information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.
To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

Benefits of the study

27. There may be a direct benefit to you from being in the study.

By joining the study, you will be part of the search for ARVs that may be better for adolescents. We do not know if being in the study will benefit you in any way. There may be a direct benefit to you by taking part in this study, but no guarantee can be made. For example, the study drugs may lower the amount of HIV in the blood. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. It is also possible that you may receive no direct benefit from this study. Information learned from this study may help other adolescents who have HIV.

You will have regular visits here and frequent checks on your health, including tests for amount of HIV in your blood, called viral load. It is possible that the study ARVs will slow your HIV infection. Information learned from this study may help other adolescents with HIV.

Other information about the study

28. There are no costs from being in the study.

There are no costs to you for study visits, CAB, RPV or procedures.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).]

29. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.
A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your study information may be given to other authorities if required by law. [Sites add more specific detail here as needed; example follows:] For example, we are required to report any significant risk of harm to you or others.

30. If you get sick or injured, contact us immediately.

Your health is important to us. We will make every effort to protect your well-being and minimize risks. It is possible, however, that you could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat you or tell you where you can get treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through [site name or] the U.S. National Institutes of Health.

**Whom to contact**

31. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

- If you have any health or other problems that may be related to study participation:
  [insert name and telephone number of investigator or other study staff]

- If you want to leave the study:
  [insert name and telephone number of investigator or other study staff]

**Signatures**

If you agree to participate in this study, please sign or make your mark below.

Before deciding whether to participate in this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to join.

If you decide to join, we will tell you any new information from this study or other studies that may affect your willingness to stay in the study. You are welcome to ask questions or request more information at any time. If you want the results from this study, please tell the study staff.

You do not give up any rights by signing this form.
[Insert signature blocks as required by site IRB/EC policies.]

Signature blocks for participants of legal age to provide independent informed consent

_______________________________  _______________  ____________________________  ____________________________
Participant’s Name (print)                  Participant’s Signature and Date

_______________________________  ____________________________
Study Staff Conducting                  Study Staff Signature and Date
Consent Discussion (print)

_______________________________  ____________________________
Witness’s Name (print)                  Witness’s Signature and Date
(As appropriate)
Appendix III-B: Sample Informed Consent Form for Participation in Cohort 2
for adolescents who can provide independent informed consent for study participation

IMPAACT 2017

Version 2.0, dated 16 August 2018

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

You are being asked to take part in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide to participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the study

This study is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and [insert site name]. The person in charge of the study at [insert site name] is [insert name of IoR].

The study is being done to test two anti-HIV medicines (antiretrovirals or ARVs) in adolescents 12 to less than 18 years old who have HIV. The study ARVs are called cabotegravir (CAB) and rilpivirine (RPV). HIV is the virus that causes AIDS.

The study will include up to 155 adolescents from the United States. There will be two groups of adolescents, called Cohort 1 and Cohort 2. This form is about Cohort 2. Participants in Cohort 2 will be in the study for 2 to 3 years. In Cohort 2, participants will get study product for 96 weeks (about 2 years). After 96 weeks, participants will have the option to continue getting the study product. If you choose to continue getting the study product, you will not have any additional study visits. If you choose to stop getting the study product, you will enter long-term follow-up and continue having study visits for an additional 48 weeks (about 1 year).

The United States National Institutes of Health and the company that makes CAB and RPV, ViiV Healthcare, are paying for this study.

1. The study is testing CAB and RPV in adolescents.

People with HIV usually take a combination of ARVs daily to stay healthy. There are not as many ARVs available for adolescents as for adults because many ARVs have not yet been tested in adolescents. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV when taken as pills and when given as shots in adolescents. The pills are taken every day. The shots are given every 4
week. The shots are being developed because it can be difficult to take pills every day, and some people may prefer to have the shots rather than taking pills.

RPV pills (25mg taken once daily) have been shown to be safe and effective for both adults and adolescents 12 years and older with HIV. These pills are already approved by the US Food and Drug Administration (FDA) for adults and adolescents with HIV.

RPV shots (600mg), CAB pills (30mg), and CAB shots (400mg) are now being tested in adults with HIV. This will be the first study of these ARVs in adolescents. So far, the testing in adults has shown that RPV shots, CAB pills, and CAB shots work as well as other ARVs that are approved. However, because these ARVs are still being tested, there may be some effects that we do not know about yet.

This study will test the effects of these ARVs in adolescents. The study will look at whether these ARVs:
- Are being given at the correct dose for adolescents
- Are safe and well-tolerated
- Can control HIV in adolescents as well as other ARVs

The study will also look at how willing adolescents are to take these ARVs.

Cohort 1 of this study was done first to test CAB and RPV pills when taken for about 1 month followed by CAB and RPV shots when taken for about 2 months. Cohort 2 is now being done to test CAB and RPV pills taken together, followed by CAB and RPV shots taken together for up to two years. Cohort 2 will look at whether these study ARVs are safe and can control HIV when adolescents stop taking their previous ARVs. More information about the study and CAB and RPV is given in the rest of this form.

2. Only adolescents who are eligible can participate in the study.

If you decide to join the study, we will first do some tests to find out if you are eligible. More information about the tests is given in #4 (see below). If you are eligible, you will be entered in the study. If you are not eligible, you cannot be entered in the study.

3. It is your decision whether or not you join the study.

Deciding to join the study is voluntary (your choice). You may choose to join or not join. If you choose to join, you can change your mind and leave the study. Your choices will have no effect on the medical care you would normally receive. Your access to services, and the benefits and rights you normally have, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can bring other people here to learn about the study with you.

*No matter what you decide about the study, it is important for you to keeping taking ARVs. This is the best known way for you to stay healthy.*
**Finding out if you are eligible**

4. **We will ask questions, examine you, and discuss the study requirements with you.**

To find out if you are eligible for the study, we will:

- Review your medical records.
- Ask questions about you, your health, and the medications you take.
- Talk with you about birth control (ways to prevent pregnancy).
- Talk with you about the study requirements and if you are able to meet these requirements.
- Do a physical exam. This will include looking at your genitals to see your stage of development. For girls, this will also include looking at your breasts.
- Do an electrocardiogram (ECG). This is to test how well your heart is working.
- Draw about 17-23mL (about 3-5 teaspoons) of blood for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Confirm that you have HIV. There are certain HIV tests that are required for this study. If the required tests are not in the medical records, we will do the tests that are needed.
  - Check the amount of HIV in your blood. This is called your HIV viral load.
  - Some blood will be saved for later testing for resistance to ARVs. This test shows whether different ARVs may work against the HIV in your blood.

These procedures will take about 4 hours [here and throughout this form, sites may modify the expected visit duration as needed].

5. **For girls, we will also test for pregnancy.**

Girls in this study cannot be pregnant. Girls should not join this study if they are pregnant or intend to become pregnant within 30 days after stopping the study ARV pills or within 48 weeks after stopping the study shots. Because the effects of the study ARVs on unborn babies are unknown, you should not become pregnant while in this study. For all girls in the study, we will collect urine or blood to test for pregnancy. There are certain effective methods of birth control that girls who are able to become pregnant must use while in this study. These effective methods must be continued for 30 days after stopping the study ARV pills, or for at least 48 weeks after stopping the study ARV shots. Girls who are able to become pregnant, must agree to use these methods in order to take part in the study. We will help make sure you can get effective methods by providing them here in the clinic or offering a referral. At study visits when you will receive study medicines (either the pill or shot), we will need to confirm that you are using effective birth control before giving you the study medicines.

Girls who become pregnant during the study will stop taking the study medicines and enter the long-term safety follow-up phase of the study (see #15 below). We will also contact you to find out the outcome of the pregnancy even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. You must give us permission before we can share these results with your parents/guardians. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.]

If you are pregnant, your doctor may report your pregnancy to the Antiretroviral Pregnancy
Registry. The Antiretroviral Pregnancy Registry assists patients and doctors in gauging potential benefits and risks of treatment; however, the registry does not collect any identifying information about you, such as your name, initials, contact information, or date of birth.

6. **We will tell you if you are eligible.**

We will give you the results of all procedures and explain the results to you. We will tell you about getting care, treatment and any other services you may need. While waiting for the results, it is important for you to keep taking your usual ARVs.

If you are not eligible for the study for any reason, we will tell you this. You will not be entered in the study. You can and should continue to receive medical care and treatment outside of the study. We will tell you more about getting this care and treatment and any other services you may need.

If you do not enter the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If you are eligible for the study, you will be entered into the study.

**Entering the study**

7. **If you are eligible, you will enter the study**

On the day you enter the study we will:
- Review your medical records.
- Talk with you about your ARV use.
- Talk with you about preventing pregnancy.
- Ask you questions about what you think about CAB and RPV
- Do a physical exam.
- Draw between 20mL (about 4 teaspoons) of blood for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Check how much the virus has affected your ability to fight the virus. This is called CD4 cell count.
  - The tests will check your HIV viral load. Some blood will also be saved for later resistance testing.
- For girls we will collect urine or blood for a pregnancy test

At the study entry visit we may also do an ECG to look at your heart. This will only be needed if you enter the study more than 2 weeks after your first visit.

At this visit, you will stop taking your usual ARVs and start taking CAB and RPV pills. We will give you the pills and explain how to take them. You will take your first dose at the visit.

This visit will take about 4 hours.

**Being in the study**

8. **After entering the study, participants take CAB and RPV pills for 4-6 weeks and then switch to CAB and RPV shots.**
For participants in Cohort 2, there are three phases of the study. All participants will take part in Cohort 2-Phase 1. Only those who are eligible will take part in Cohort 2-Phase 2. Participants who take part in Cohort 2-Phase 2 will also take part in Cohort 2-Phase 3, called the long-term follow-up safety phase.

In Cohort 2-Phase 1, you will take CAB and RPV pills. The pills must be swallowed whole. They cannot be broken or crushed. They should be taken with food. This phase lasts for about 4-6 weeks. You will have 3 visits during this time. At these visits, we will check on how you are doing while taking the pills (see #9 for more information). We will also check on whether you are eligible for Cohort 2-Phase 2.

If you are eligible for Cohort 2-Phase 2, you will stop taking CAB and RPV pills and start getting CAB and RPV shots. This phase lasts 2-3 years. You will have 25 visits over about two years and may have another 5 visits over one additional year. You will get shots at 23 visits during the first two years. At each of these 23 visits, you will be given one shot of CAB and one shot of RPV. Each shot is about 3mL (about 1 teaspoon). The shots are given in the buttocks (bottom “cheeks”). The shots may be given on the same side of the buttocks or on different sides. The shots are long-acting, meaning the medicine stays in your body for a long time. They are given every 4 weeks. At all of these study visits, we will check on how you are doing while getting the shots (see #11 for more information).

After Cohort 2-Phase 2, you will have the option to continue getting the long-acting injections or to stop getting them. If you no longer want to get the injections, you will take part in Cohort 2-Phase 3, the long-term follow-up safety phase of the study. This phase lasts about 48 weeks. You will also go back to taking your usual (pre-study) ARVs. There will be 4 or 5 visits during long-term follow up (see #15 for more information).

9. In the Cohort 2-Phase 1, you will have 2 visits.

Visits in this phase will be scheduled 2 weeks apart. [Sites to modify] Each visit will take about 1-3 hours. At each of these visits, we will:

- Review your medical records.
- Talk with you about your ARV use
- Do a physical exam.
- Talk with you about preventing pregnancy.
- For girls, we will collect urine or blood to test for pregnancy.
- Remind you to bring the oral CAB and oral RPV to the study clinic.

At two of these visits (Week 2 and Week 4a), we will draw about 5mL (about 1 teaspoon) of blood for tests. These tests will check your blood cells and how well your liver and kidneys are working.

At the second visit (Week 2), we will draw about 12mL (about 2-3 teaspoons) blood for tests. This test will check your HIV viral load. Some blood will be saved for later resistance testing.

At the Week 2 visit we will also test the amount of CAB and RPV in your blood. This is called a pharmacokinetic (PK) test. At this visit, we will ask you when your child took CAB or RPV in the past three days. [Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection.] For three days before this visit, you must be sure to give your child CAB and RPV on time and in the morning. This is very important. We will help you remember this before the visit.

We will need to draw your blood two times during the visit, before and after taking CAB and RPV. We will remind you to not to take CAB or RPV before coming to this visit. When you come to the visit, we will draw
your blood, then you will take CAB and RPV, and then we will draw your blood again, about two hours later. Each time we will draw 4mL (less than 1 teaspoon), for a total of 8mL (about 2 teaspoons).

Study staff will let you know when these procedures will occur ahead of time.

10. We will tell you if you are eligible for the Cohort 2-Phase 2.

At the Week 4b visit, we will determine if you are eligible for Cohort 2-Phase 2. At this visit we will:
- Review your medical records.
- Talk with you about your ARV use.
- Do a physical exam.
- Ask you questions about what you think about CAB or RPV.
- Talk with you about preventing pregnancy.
- Draw about 12mL (about 2-3 teaspoons) blood for tests. These tests will check your HIV viral load. Some blood will be saved for later resistance testing.
- For girls, we will also collect urine or blood to test for pregnancy.
- [Sites: modify language as appropriate to align the three prior doses with the timing (morning or evening) of the Week 4b pre-dose PK sample collection. Remind you to take the oral CAB and oral RPV in the morning for the three days before this visit.]

If you are not eligible, you will stop taking oral CAB and oral RPV and will start taking your previous ARVs again. If you did not participate in Cohort 1, you will complete a final study visit about 4 weeks after your last oral dose (see #14 for more information). If you also participated in Cohort 1 and received shots of CAB or RPV in Cohort 1-Phase 2 in, but are not eligible to get the shots of CAB and RPV in Cohort 2, you will stop taking oral CAB and oral RPV and will enter into Cohort 2-Phase 3 long-term follow-up (see #15 below).

If you are eligible, you will take your last dose of oral CAB and oral RPV at the Week 4b visit. At this visit, we will also give you the first shot of CAB and the first shot of RPV. We will remind you not to take oral CAB and RPV before coming to this visit. You will take oral CAB and RPV at the study clinic before the first shot of CAB and the first shot of RPV.

At this visit, we will also look closely at the amount of CAB and RPV in your blood. To do this, we will need to draw your blood two times during the visit, before taking oral CAB and RPV and after getting a shot of CAB and a shot of RPV. When you come to the visit, we will draw your blood, then you will take oral CAB and RPV and get a shot of CAB and RPV, and then we will draw your blood again, about two hours later. Each time we will draw 4mL (less than 1 teaspoon) for a total of 8mL (about 2 teaspoons).

11. In Cohort 2-Phase 2, you will have 26 visits (Weeks 4b-96).

The first visit in Cohort 1-Phase 2 will be the Week 4b visit, which is described in #10 above. Most of the other visits in this phase will be scheduled about 4 weeks apart. [Sites to modify] Each visit will take about 1-3 hours. At each of these visits, we will:
- Review your medical records.
- Talk with you about preventing pregnancy.
- Do a physical exam. At two of these visits (Weeks 24 and 96), this exam will include examination of your genitals to see the stage of development. For girls, this will also include looking at the breasts.

At 23 of these visits (Weeks 8-24 and 28-96) we will:
- Give a shot of CAB and a shot of RPV.
• For girls, we will also collect urine or blood to check for pregnancy.

At 16 of these visits (Weeks 5, 8-24, 28-48, 60, 72, 84, and 96) we will draw about 5mL of blood (about 1 teaspoon) for tests. These tests will check:
• Your blood cells
• How well your liver and kidneys are working

At 15 of these visits (Weeks 8-24, 28-48, 60, 72, 84, and 96) we will draw about 12mL of blood (about 2-3 teaspoons) for tests. These tests will check:
• Your HIV viral load.
• Some blood will be saved for later resistance testing.

At 13 of these visits (Weeks 5, 8-24, 25, 36, 48, 60, 72, 84, and 96), we will also draw about 4mL of blood (less than 1 teaspoon) of blood to look at the amount of CAB and RPV in the blood.

At 4 of these visits (Weeks 24, 48, 72 and 96) we will draw about 3mL of blood (about 1 teaspoon) to check your CD4 count.

At 5 of these visits (Weeks 8, 12, 24, 48, and 96) we will ask you questions about getting the shots of CAB and RPV.

At 5 of these visits (Weeks 8, 24, 48, 72, and 96) we may also talk with you about how you are doing with the visit schedule.

At 2 of these visits (Week 48 and 96) we will also talk with you about preventing pregnancy.

Study staff will let you know when these procedures will occur ahead of time.

12. In-depth phone interviews

We are very interested to understand what adolescents think about getting their ARV’s as shots. You will be asked if you would like to complete an in-depth phone interview. If you would like to take part in the interview, then you may be contacted to have the interview after getting the sixth shot of CAB and RPV.

If contacted, this interview will take approximately 1-2 hours, and will ask about how you feel about having shots of CAB and RPV. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about them receiving the shots. The interview may take place at or in between the Week 24 through 96 visits or during the long-term follow-up safety phase. The interview will only take place once. The interview will be audio recorded and written down in a report. Your name will not be included in the report. Not all participants will be contacted for the interview. You do not have to do the interview to take part in this study.

We may also ask your parent or caregiver to complete an in-depth interview. This interview would ask them how they felt about you having shots of CAB and RPV.

13. Adolescents may have an extra visit if their HIV is not controlled.

Participants will have viral load tests at almost all visits to check the amount of HIV in the blood. If tests show that the viral load is higher than expected (above 200 copies/mL) you will have repeat testing. This may occur as part of another study visit or may occur as an extra study visit.
The extra visit will take about 1-2 hours. At this visits we will:

- Review your medical records.
- Do a physical exam.
- Draw about 16mL (about 3 teaspoons) of blood for tests. The tests will:
  - Check your HIV viral load.
  - Check the amount of CAB and RPV in the blood.
  - We will save some blood for later resistance testing.
- Talk with you about preventing pregnancy.
- For girls, we will also collect urine or blood to check for pregnancy.

If the repeat test also shows an increased amount of HIV in your blood, you will stop taking the study product and start taking your previous ARVs again. If you were getting shots of CAB and RPV, you will enter long-term follow-up (more information in #15 below).

14. **If you are not eligible to receive shots of CAB and RPV you will stop the study early.**

If you are not eligible to get shots of CAB and RPV, you will stop taking oral CAB and oral RPV and will complete a final study visit about 4 weeks after your last oral dose.

During this visit, we will:

- Review your medical records.
- Do a physical exam. This will include examination of your genitals to see the stage of development. For girls, this will also include looking at the breasts.
- Draw blood for tests. This would be about 17mL of blood (about 3-4 teaspoons) for these tests. These tests will check:
  - Your blood cells.
  - How well your liver and kidneys are working.
  - Your HIV viral load.
  - Some blood will also be saved for later resistance testing.
- Talk with you about preventing pregnancy.
- For girls, we will also collect urine or blood to check for pregnancy.
- Ask you questions about taking the oral CAB and oral RPV.
- We will talk with you about your ARV use.

If you also participated in Cohort 1 and received shots of CAB or RPV in Cohort 1-Phase 2, but are not eligible to get the shots of CAB and RPV in Cohort 2, you will stop taking oral CAB and oral RPV and will enter into Cohort 2-Phase 3 long-term follow-up (see #15 below).

15. **If you stop the shots of CAB and RPV early or after the Week 96 study visit, you will enter long-term follow-up.**

If you stop the shots of CAB and RPV early, or choose to not continue to get the shots of CAB and RPV after the final visit (Week 96) in Cohort 2-Phase 2, you will enter Cohort 2-Phase 3, also called the long-term follow-up safety phase after the last shot of study product. For females, if you become pregnant, you will enter this phase of the study after your last dose of study medicine, whether the pill or the shot. At this time, you will stop getting shots of CAB and RPV. You will start taking your previous ARVs again. There will be 4 or 5 additional visits during the long-term follow up.

These visits will be scheduled 4, 12, 24, 36 and 48 weeks after your last shot of CAB and RPV. Each of these visits will take about 1-3 hours. At these visits, we will:
• Review your medical records.
• Talk with you about preventing pregnancy.
• Do a physical exam. At the final long-term follow-up visit, this will include examination of your genitals to see the stage of development. For girls, this will also include looking at your breasts.
• Draw blood for tests. This would be about 21mL of blood (about 4 teaspoons) for these tests. These tests will check:
  o Your blood cells.
  o How well your liver and kidneys are working.
  o Your HIV viral load.
  o The amount of CAB and RPV in the blood.
  o Some blood will also be saved for future resistance testing.
• For girls, we will also collect urine or blood to check for pregnancy.
• At two of these visits (4 weeks and 48 weeks after your last shot of CAB and RPV) we will talk with you about your ARV use.
• At the final visit (48 weeks after your last shot of CAB and RPV), we will also ask you questions about getting shots of CAB and RPV.

For participants who complete the Week 16 visit in Cohort 2-Phase 2, the first long-term follow-up visit will be skipped entirely. The Week 16 visit and the first long-term follow-up visit are very similar and do not need to be conducted twice.

16. **The tests for the amount of CAB and RPV in your blood will be done at different laboratories.**

We will do most of the tests of blood or urine here at our laboratory. We will give you the results of most of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

We will also draw blood to check the amount of CAB and RPV in your blood. This is called a pharmacokinetic (PK) test. The test will be done at other laboratories in the United States or in Ireland. We will not usually give you the results of this test during the study.

17. **We may take you off of the study.**

We may take you off the study ARVs if:
• You are not able to come to the study visits or we determine that you cannot meet the study requirements.
• You are not able to take the study ARVs.
• The study ARVs are not controlling the HIV in your blood.
• Continuing the study ARVs may be harmful to you.
• You request to stop the study ARVs.

If you stop the oral study ARVs early, we will ask you to come back to the clinic about four weeks after you stop the oral study ARVs (see #14 above). You will not have any other visits after this.

If you stop the ARV shots early, we will ask you to come back to the clinic for four or five additional study visits for long-term follow-up (see #15 above). You will not have any other visits after these four or five visits.

We may also take you off the study early if the study is stopped for any reason.
The study cannot provide other types of ARVs, but we will give information, counseling, and referrals to where you can get care and treatment needed. We will help make sure you can get ARVs from outside of the study. If the study stops early, every effort will be made to make certain that there is no interruption in your therapy.

18. Please tell us if you want to leave the study.

You are free to leave the study at any time for any reason. The care that you receive at this clinic will not be affected, but it is important for us to know about your decision.

If you stop the study ARVs, we may ask you to return to the study clinic for additional study visits described in #14 and #17 above. If you stop the study early, we may ask that you have one final study visit.

We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

After the study

19. Receiving the study ARVs after the study is over.

As you come to the end of the study, we will work with you to plan for your care and treatment outside the study. It is important that we plan for this in advance, so that there is no gap in your taking ARVs as you finish the study. Taking ARVs without interruption is the best known way for you to stay healthy.

We will tell you where you can go to receive needed care and treatment after you finish the study. If you are gaining benefit from the injection ARVs given in the study, the company that is providing these ARVs (ViiV) will try to provide these injection ARVs to you. They will be provided until they are otherwise available locally, until you are no longer gaining benefit, or if the company decides to stop studying the ARVs. However, there is no guarantee this will be possible. If this is not possible, you will need to switch to other oral ARVs that are available locally. We will explain the options to you and help ensure your access to ARVs outside the study. We will also contact you again within the first four weeks after you finish the study to confirm that you are getting ARVs.

Risks of the study

Taking part in this study may involve some risks and discomfort. The risks are different for each phase of the study. Cohort 2-Phase 1 risks include: risks from blood draws, risks from the study pills (CAB and RPV), and risks to your privacy.

Cohort 2-Phase 2 risks include: risks from blood draws, risks from receiving the injection, risks from the study pills (CAB and RPV) and the study shots (long-acting CAB and RPV), risks of switching ARVs and risks to your privacy.

Cohort 2-Phase 3 risks include: risks from blood draws, and risks to your child’s privacy.

20. Risk from blood draws

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.
21. Risk from receiving the injection

People in other studies who have received the CAB LA and RPV LA shots said they had pain, skin irritation, skin redness, bumps, swelling, itching, bruising at the spot where they got the shot. Most reactions go away in a week or less but sometimes they can last a long time. Most people usually do well with them and rarely need to stop the drug.

The shots will be given in the muscles of your buttocks. The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve.

The risks of this are not well understood, but could make drug levels too low or too high. If too low the drug may not work against your HIV. If RPV is too high, there could be a change in your heart beat, which in severe cases can be life-threatening. Everything possible will be done to decrease this risk, including watching you for problems during the study. If your doctor thinks that the injection was not given the right way, you might be asked to stay in the clinic up to [sites to modify] 2 hours after the injection to watch how you are doing and extra tests may be needed to be sure you are safe. If you are worried about this risk, talk to your doctor.

22. There are risks from the study ARVs

All ARVs can cause side effects. This includes the ARVs you are currently taking and the ARVs that are given in the study. Some side effects are minor; others can be severe. Some side effects are common; others are rare. Some people who take ARVs have some of the side effects. Other people have different side effects, or no side effects.

The most common and most serious side effects of the study ARVs, CAB and RPV, are listed below. This is based on what we know now about CAB and RPV. There may be other side effects that we do not know about now. This may be especially true for adolescents, because this is the first study of CAB and RPV in adolescents.

This form does not list all possible side effects of all ARVs. If you join the study, we will tell you more about the ARVs you will be taking. At each study visit, we will check on whether the ARVs may be causing side effects. We will also tell you what to do if you have side effects. If you have questions or concerns at any time, please tell us.

23. Some side effects from the CAB pills and the CAB LA

Many people have received CAB pills or the CAB LA shot in other studies. The table below lists side effects from other studies of CAB with people who have HIV. It is not known if CAB, other drugs or the patient’s other health problems caused or affected these. Some of these are the same side effects as RPV (see #24 below).

Common Side Effects of CAB
Very Common Side Effects of CAB

- Nausea (feeling sick to the stomach)
- Diarrhea or loose stools
- Runny nose, sore throat/Upper respiratory tract infection
- Headache
- Fever
- Lack of energy

Common Side Effects of CAB

- Rash
- Itching
- Vomiting (being sick)
- Stomach pain and discomfort
- Problems sleeping
- Abnormal dreams/nightmares
- Feeling light headed
- Depression
- Passing gas or wind
- Joint or muscle pain
- Increase in the level of enzymes made in the muscles (creatine phosphokinase)

The following effects have also been seen in some of the people who received CAB pills or the CAB LA shot in other studies:

**Abnormal liver tests:**

A small number of people across all studies (just over 1% of 1644 participants as of April 2017) had abnormal liver tests requiring them to stop CAB. Some abnormal liver tests were explained by other things such as a new virus infection, like Hepatitis A, B or C. Very few people did not have another possible reason so it is possible that a mild form of liver damage happened from taking CAB. The liver tests got better after stopping CAB, showing that any damage was temporary.

Blood tests to check the health of your liver will be done during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other action is needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual ARVs.

**Seizures/convulsions:**

Seizures have been seen (rarely) in people with and without HIV. They are not thought to be caused by CAB, but the study staff will ask you about them.

In other studies, two people without HIV had a history of seizures (epilepsy), and had a seizure about 3 months and 9 months after starting CAB. One other person with HIV but without a history of seizures, had seizures about one year after starting CAB. This participant had a long period of seizures without medical treatment and died. It is not known if CAB was part of the reason for seizures in these people. If you have a history of seizures, please let your study doctor know.

**24. Some side effects from the RPV pills and the RPV LA**

The following side effects have been seen with rilpivirine in HIV-infected patients in clinical trials. Oral RPV (Edurant) is a marketed drug and many more people have received Edurant. The side effects of Edurant are more
known than the side effects for CAB, and more known than the side effects of RPV LA. Many people have taken part in studies and received RPV LA, and some also received CAB LA. The following side effects have been seen in studies in people with HIV taking RPV.

**Common Side Effects of RPV**

<table>
<thead>
<tr>
<th>Very Common Side Effects of RPV</th>
<th>Common Side Effects of RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems sleeping</td>
<td>Rash</td>
</tr>
<tr>
<td>Headache</td>
<td>Depression</td>
</tr>
<tr>
<td>Feeling light headed</td>
<td>Abnormal dreams</td>
</tr>
<tr>
<td>Nausea (feeling sick to the stomach)</td>
<td>Lack of energy</td>
</tr>
<tr>
<td>Increase in the level of liver enzymes</td>
<td>Vomiting</td>
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<td></td>
<td>Sleepiness</td>
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<td></td>
<td>Decreased appetite</td>
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<tr>
<td></td>
<td>Stomach pain and discomfort</td>
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<tr>
<td></td>
<td>Dry Mouth</td>
</tr>
<tr>
<td></td>
<td>Sleep problems</td>
</tr>
</tbody>
</table>

The following effects have also been seen in some of the people who received RPV in other studies:

**Abnormal blood tests:**

Other changes in blood tests have also been observed. People with hepatitis B or C or increased in liver tests showing possible liver damage before starting RPV may have worse liver tests while taking RPV. A few cases of liver problems have also been seen in people taking RPV who did not already have any liver problems.

Sometimes allergic reactions can affect body organs, like the liver and cause liver problems which can lead to liver failure. Contact your study doctor right away if you have any of the following signs or symptoms of liver problems:

- **Yellowing of the skin or whites of the eyes**
- **Dark or tea colored urine**
- **Pale colored stools/bowel movements**
- **Nausea/vomiting**
- **Loss of appetite**
- **Pain, aching or tenderness on the right side below the ribs**

Blood tests to check the health of your liver will be done during the study. Your study doctor will tell you if you need to stop taking the study drugs or if other action is needed. If you stop taking the study drug, you may be able to re-start the study drug or you may need to change your usual ARVs.

**Skin Rash:**

Most rashes were mild or moderate, and happened within the first 4 weeks of taking RPV. Most of rashes got better after one week, and the people did not need to stop taking RPV. However, the study ARVs will need to be stopped for some types of moderate rash and all types of severe rash, which can be life-threatening. If this happens to you, you will need to come for extra study visits to monitor your health. Some people with rash may
also have other signs and symptoms of allergic reaction.

If you have any type of rash or other skin problems during the study you must tell your study doctor right away, and the doctor may tell you to stop taking CAB and/or RPV.

25. There may be other possible risks from the study ARVs.

The study ARV shots stay in your body for a long time

The shots you get in this study are long acting, meaning they stay in your body for a long time. In most people the drugs will no longer be in the body one year after an injection, while in some people low levels of CAB and RPV may still be in the body after one year. If you develop a side effect to the study drug after the shot, there will be no way to remove the drug from your body. If you get a shot of CAB or RPV, we will monitor your health for 48 weeks after your last shot. If you develop a symptom from these drugs while the drugs are still in your body, every effort will be made to treat the side effects. The amount of drug will decrease overtime and will eventually disappear.

While the amount of study drugs in your body decrease slowly over time after you stop getting shots, the study drugs could stop working against your HIV. When stopping long acting HIV drugs, it will be very important to start taking other HIV medications, as your study doctor tells you, so your HIV medications do not stop working against your HIV.

Risk of switching ARVs

If you join this study, you will stop taking the ARVs you are currently taking, and start taking ARVs given by the study. The study ARVs could cause side effects that you would not have from the ARVs you are currently taking. The study ARVs also may not work as well as the ARVs you are currently taking. For example, the study ARVs may not work as well to control the amount of HIV in your body. We will test your HIV viral load at most study visits to check on this. If your viral load is higher than expected, you will have repeat testing, and your use of the study ARVs may be stopped (see #13 above).

Risk of resistance

By stopping your previous ARVs and switching to the study ARVs, you could develop resistance. This could happen if the study ARVs don’t work as well to control the amount of HIV in your body. Resistance means that the ARVs may not work against HIV if these ARVs are taken again in the future. To stop resistance, it is important that you take the ARVs as instructed, and do not miss any doses.

Mental Illness

Some people with HIV sometimes have feelings of depression or may have thoughts of hurting or killing themselves (suicide). A small number of people being treated with drugs called integrase inhibitors [INIs] for HIV like CAB, have had suicidal thoughts and actions, particularly patients with a prior history of depression or mental health illness.

Tell the study doctor if you have a history of mental health illness. If you have thoughts of hurting or killing yourself or have any other unusual or uncomfortable thoughts or feelings during this study, you should tell the study doctor or go to the nearest hospital right away.

Possible effects on pregnancy or unborn babies
HIV and ARVs may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others. We do not yet know if CAB or RPV are safe in pregnancy.

There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug.

Early results from one large study in Botswana showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects of the brain or spine in the new baby. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.

CAB is not the same drug as DTG. We do know that CAB and DTG belong to the same class of medications and work in a similar way to treat HIV infection. We do not know if CAB can cause brain or spine defects in babies.

Girls who are able to become pregnant must agree to use certain effective methods of birth control to be in this study (see #5 above). If you become pregnant during the study, please let us know right away.

*Immune reconstitution syndrome*

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases may occur soon after starting combination ARVs but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or if you notice that any existing symptoms are getting worse after starting the ARVs, tell your doctor immediately.

*Abnormal placement of body fat and wasting*

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

26. There could be risks of disclosure of your information.

We will make every effort to keep your information private and confidential. Study records and specimens will be kept in secure, locked locations. All specimens and most records will be labeled only with a code number. However, your name will be written on some records.

Despite our best efforts to keep your information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.
To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

**Benefits of the study**

27. There may be a direct benefit to you from being in the study.

By joining the study, you will be part of the search for ARVs that may be better for adolescents. We do not know if being in the study will benefit you in any way. There may be a direct benefit to you by taking part in this study, but no guarantee can be made. For example, if you get shots of CAB and RPV, you might prefer having monthly shots instead of taking daily pills. The study ARVs may have fewer side effects than the previous ARVs you were taking. The study drugs may also lower the amount of HIV in the blood. There may also be benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. It is also possible that you may receive no direct benefit from this study. Information learned from this study may help other adolescents who have HIV.

You will have regular visits here and frequent checks on your health, including tests for amount of HIV in your blood, called viral load. It is possible that the study ARVs will slow your HIV infection. Information learned from this study may help other adolescents with HIV.

**Other information about the study**

28. There are no costs from being in the study.

There are no costs to you for study visits, CAB, RPV or procedures.

*Insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).*

29. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.
A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your study information may be given to other authorities if required by law. [Sites add more specific detail here as needed; example follows:] For example, we are required to report any significant risk of harm to you or others.

**30. If you get sick or injured, contact us immediately.**

Your health is important to us. We will make every effort to protect your well-being and minimize risks. It is possible, however, that you could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat you or tell you where you can get treatment. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through [site name or] the U.S. National Institutes of Health.

**Whom to contact**

**31. If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

- If you have any health or other problems that may be related to study participation:
  [insert name and telephone number of investigator or other study staff]

- If you want to leave the study:
  [insert name and telephone number of investigator or other study staff]

**Signatures**

If you agree to participate in this study, please sign or make your mark below.
Before deciding whether to participate in this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to join.

If you decide to join, we will tell you any new information from this study or other studies that may affect your health, welfare, or willingness to stay in the study. You are welcome to ask questions or request more information at any time. If you want the results from this study, please tell the study staff.

You do not give up any rights by signing this form.
[Insert signature blocks as required by site IRB/EC policies.]

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’s Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
</tr>
</tbody>
</table>
Appendix III-C: Sample Informed Consent Form for Specimen Storage and Future Use  
for adolescents who can provide independent informed consent for study participation  

IMPAACT 2017  

Version 2.0, dated 16 August 2018  

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

You have decided to join the study named above. As part of the study, you will have blood and urine collected. After these samples are tested for the study, some samples may be left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

This form gives information about use of extra samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

1. It is your decision whether or not to allow the extra samples to be used.

You are free to say yes or no, and to change your mind at any time. Your decision will not affect your participation in the study. If you say no, all extra samples will be destroyed.

2. If you agree, your extra samples will be kept in a repository.

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. If you agree to have extra samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept [sites may insert time limits or additional site-specific requirements here if required by local authorities].

3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, the extra samples could also be used for research that looks at your genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people’s genes can help explain why some people get a disease while others do not. Your samples would only be used to look at genes related to HIV and the immune system.

Any research done with the extra samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.

The research done with extra samples is not expected to give any information relevant to your health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your study records.
4. **There is little risk to you.**

When extra samples are used for research, they are labeled with a code number only. To protect your privacy, no names are used. However, information such as age, gender, HIV status, and other health information may be linked to the samples. Information on the ARVs you received in the study may also be linked to the samples.

There may be some risks from tests of your genes. If others found out the results of these tests, they could treat you badly or unfairly. However, this is almost impossible because the results will not be given to the study staff, or to you, and will not be in your study records.

5. **There may be no benefit to you.**

By allowing extra samples to be used for research, you will be part of the search for new information that may benefit people with HIV in the future. However, the research done with the extra samples is not expected to directly benefit you in any way.

6. **You will not be paid for use of your samples.**

There is no cost to you for use of your extra samples. The samples will not be sold, and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with you.

7. **Information from research using extra samples may be reviewed by groups that oversee the research.**

These groups include:
- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research
- Other local, US, or international regulatory entities

The people who do research with the extra samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with the extra samples may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

8. **If you have questions, concerns, or problems at any time, use these contacts.**

- If you have questions about use of your extra samples:
  [insert name and telephone number of investigator or other study staff].

- If you later change your mind about use of your extra samples:
  [insert name and telephone number of investigator or other study staff].

- If you have questions about your rights as a research participant or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization].
Signatures

Before deciding whether your extra samples to be used for research, make sure you have read this form, or had it read to you. Make sure all of your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination if the level of risk to children in the categories specified in 45 CFR 46.404-407. Separate consent decisions must be documented for genetic testing].

For YOUR extra samples, write your initials or make your mark next to your choice.

__________ I allow my extra samples to be used for research on HIV, the immune system, ARVs, and other diseases. I also allow my samples to be used for tests of his or her genes.

__________ I allow my extra samples to be used for research on HIV, the immune system, ARVs, and other diseases. I do not allow my samples to be used for tests of his or her genes.

__________ I do not allow my extra samples to be used for any research.

Signature blocks for participants of legal age to provide independent informed consent

Participant’s Name (print)  Participant’s Signature and Date

Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date

Witness’s Name (print)  Witness’s Signature and Date (As appropriate)
Appendix IV: Sample Informed Assent Forms

Appendix IV-A: Sample Informed Assent Form for Participation in Cohort 1
for adolescents who cannot provide independent informed consent for study participation

IMPAACT 2017

Version 2.0, dated 16 August 2018

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

You are being asked to take part in a research study. In order for you to take part, you must give your permission. Your parent/guardian must also give their permission.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as you need to understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide to take part, you will sign or make your mark on this form. You will be offered a copy to keep.

About the study

This study is for 12-17 year olds who have HIV. The study will test two anti-HIV medicines (antiretrovirals or ARVs). The ARVs are called cabotegravir (CAB) and rilpivirine (RPV).

People with HIV take a combination of ARVs to stay healthy. There are not as many ARVs available for children and teenagers as for adults, because many ARVs have only been tested in adults. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV pills and shots. The pills are taken every day. The shots are given every 4 weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer having shots instead of taking pills.

There will be two groups in the study, called Cohort 1 and Cohort 2. This form is about Cohort 1.

What happens in the study

If you decide to take part in the study, we will check your medical records and examine you to see if you qualify. This will include looking at your genitals to see how developed you are. We will ask you and your parent/guardian questions about your health and the medications you take. We will collect blood for tests. We will also do a test of your heart called an ECG.

For girls, we will do a pregnancy test. If you are pregnant, you cannot take part in the study. Girls who are able to become pregnant must agree to use certain methods of birth control in order to take part in the study. If you become pregnant during the study, you will stop getting CAB or RPV pills or shots and will enter the long-term
follow-up safety phase of the study. We will also contact you to find out the outcome of the pregnancy, even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. You must tell us it is ok before we can share these results with your parents/guardians. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.]

We give you your test results and explain them to you. If you qualify, you can join the study. If you do not join the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

First phase of the study

The study has three phases. If you join, you will start in the first phase. You will be given CAB or RPV pills to take in addition to the other ARVs you are already taking. It is important to keep taking all your ARVs as instructed.

You will have 3 study visits over 4-6 weeks (about one month). At these visits, we will:

- Collect information from your medical records.
- Ask questions about your health, ARVs, and other medications.
- Give you a physical exam.
- Collect blood for tests. This will be done using a needle in your arm.
- For girls, collect blood or urine for a pregnancy test.
- At the first visit, we may do an ECG test to look at your heart.

Each visit will take about 1-3 hours.

At the second visit, we will look very closely at the amount of CAB or RPV in your blood. To do this, we will collect your blood different times over 24 hours (one full day). If you are taking CAB, we will collect your blood 7 times. If you are taking RPV, we will collect your blood 4 times. [Sites: modify language as appropriate to indicate procedures for the intensive PK collection: A small tube will be placed in your arm and attached to a plastic needle to draw your blood, so we do not need to stick you with a needle each time. The plastic tube may stay in place for 24 hours. You may need to stay at the clinic or hospital for up to 24 hours. If the study clinic is able, you may be able to stay at the clinic the night before and during this visit.]

Second phase of the study

At the fourth study visit, we will review all your test results to see if you qualify for the second phase of the study.

- If you do not qualify, you will stop taking CAB or RPV pills. You have one more visit about 4 weeks later. This visit will be like the other visits described above.
- If you qualify, you can enter the second phase of the study

In the second phase of the study you will have 7 study visits over 12 weeks (about 3 months). At these visits, we will:
• Collect information from your medical records.
• Ask questions about your health, ARVs, and other medications.
• Give you a physical exam. At the last visit, we will also look at your genitals again to see how developed you are.
• Collect blood for tests. This will be done using a needle in your arm.
• For girls, collect blood or urine for a pregnancy test.
• At two of these visits, we may do an ECG test to look at your heart.

Each visit will take about 1-3 hours.

During the second phase of the study, you will not take CAB or RPV pills. Instead, you will be given shots of CAB or RPV. The shots will be given 3 times (4 weeks apart, about once per month). You will get one shot in the buttocks (bottom, “cheeks”) each time. You will keep taking your other ARVs while getting the shots.

You may also be contacted to answer questions over the phone about how you feel about the shots.

After 12 weeks, we will review your tests to see if you are eligible for Cohort 2.
• If you do not qualify, or if Cohort 2 isn’t ready yet, you will stop getting shots CAB or RPV. You will enter into the third phase, which is also called the long-term follow-up safety phase of the study. This is described below.
• If you qualify, and when Cohort 2 is ready, you can enter Cohort 2.

_Long-term follow-up safety phase of the study_

You will have 4 or 5 study visits over 48 weeks (about 1 year). The visits will be like the visits described above.

You will not be given CAB or RPV pills or shots. You will keep taking your other ARVs.

_Risks of the study_

Having blood collected may cause pain, bleeding, bruising, swelling, or infection where the needle goes in your arm.

Having shots of CAB or RPV may cause pain, irritation, redness, bumps, swelling, itching, or bruising on the buttocks (where the shot is given). When CAB and RPV are given as shots, they stay in the body for much longer than when CAB and RPV are taken as pills.

CAB and RPV can cause other side effects. These side effects are common, but not everyone will have them. You may have pain, feel sick to your stomach, or vomit (throw up). You may have diarrhea. You may have a headache, fever, runny nose, sore throat, dry mouth, or rash. You may have trouble sleeping or a lack of energy. You may not want to eat as much as you usually do. You may feel light headed or sad. You may have problems in other parts of the body, such as your liver.

We do not yet know if CAB or RPV are safe in pregnancy. Early results from one study showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects in the new baby. These mothers were taking the drug before they knew they were pregnant. The birth defects have not been seen when mothers started taking DTG later in pregnancy. CAB is not the same drug as DTG. We do not know if CAB can cause the same defects in babies.
Girls who are able to become pregnant must agree to use certain methods of birth control to be in this study. If you become pregnant during the study, please let us know right away.

We will check for side effects at each study visit. Please tell us if you have any side effects or don’t feel well. We will also check the amount of HIV in your blood. If you have side effects, or if the amount of HIV in your blood is higher than expected, you may have extra visits. We will talk with you and your parent/guardian about this, and tell you what to do about any side effects. We will also tell you if you can keep taking CAB or RPV. In some cases, you may have to stop taking CAB or RPV.

All information collected for this study will be kept private and confidential. However, it is possible that information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stressed or embarrassed.

Other information about the study

Study records may be reviewed by study staff and groups that oversee the study. Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

[Sites may modify this paragraph to reflect local reporting requirements and legal statues: Your study information may be shared with other authorities if required by law. Public health authorities are required by law to receive information for the prevention or control of disease, injury or disability. (We must follow laws requiring the reporting of suspected child abuse and neglect).]

Benefits of the study

By joining the study, you will be part of the search for new ARVs for adolescents. The information learned in this study could someday lead to better ARVs for adolescents. However, being in this study may not be of any benefit to you.

Your rights
Taking part in this study is voluntary. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on the medical care you normally receive.

**Who to contact**

If you have questions about the study:
[insert name and telephone number of investigator or other study staff]

If you have questions about your rights or how you are treated in the study:
[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

If you have problems related to being in the study:
[insert name and telephone number of investigator or other study staff]

If you want to leave the study:
[insert name and telephone number of investigator or other study staff]

**Signatures**

*If you want to take part in this study, sign or make your mark below.*

Before deciding whether to take part in this study, make sure you have read this form, or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to take part.

We will tell you and your parent/guardian any new information that may affect your willingness to stay in the study. You can ask questions or ask for more information at any time.

You do not give up any rights by signing this form.

*[Insert signature blocks as required by site IRB/EC policies.]*

Name of Participant (print)  Signature of Participant  Date

Name of Study Staff Conducting Assent Process Name (print)  Signature of Study Staff  Date

Name of Witness (as appropriate; print)  Signature of Witness  Date
Appendix IV-B: Sample Informed Assent Form for Participation in Cohort 2 for adolescents who cannot provide independent informed consent for study participation

IMPAACT 2017

Version 2.0, dated 16 August 2018

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

You are being asked to take part in a research study. In order for you to take part, you must give your permission. Your parent/guardian must also give their permission.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as you need to understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide to take part, you will sign or make your mark on this form. You will be offered a copy to keep.

About the study

This study is for 12-17 year olds who have HIV. The study will test two anti-HIV medicines (antiretrovirals or ARVs). The ARVs are called cabotegravir (CAB) and rilpivirine (RPV).

People with HIV take a combination of ARVs to stay healthy. There are not as many ARVs available for children and teenagers as for adults, because many ARVs have only been tested in adults. ARVs can be made in different forms, such as liquids, pills, and injections (shots). The study will test CAB and RPV pills and shots. The pills are taken every day. The shots are given every 4 weeks. The shots are being developed because it can be difficult to take pills every day, and some people may prefer having shots instead of taking pills.

There will be two groups in the study, called Cohort 1 and Cohort 2. This form is about Cohort 2.

What happens in the study

If you decide to take part in the study, we will check your medical records and examine you to see if you qualify. This will include looking at your genitals to see how developed you are. We will ask you and your parent/guardian questions about your health and the medications you take. We will collect blood for tests. We will also do a test of your heart called an ECG.

For girls, we will do a pregnancy test. If you are pregnant, you cannot take part in the study. Girls who are able to become pregnant must agree to use certain methods of birth control in order to take part in the study. If you become pregnant during the study, you will stop getting CAB and RPV pills or shots and will enter the long-term
follow-up safety phase of the study. We will also contact you to find out the outcome of the pregnancy, even if the outcome occurs after leaving the study.

[Sites may modify the following paragraph to include locally appropriate language regarding disclosure of pregnancy results to parents or guardians: As soon as the pregnancy test result is available, we will go over it with you in private, without your parents/guardians present. You must tell us it is ok before we can share these results with your parents/guardians. If the test shows that you are pregnant, we will give you information on where medical care and other services can be received.]

We give you your test results and explain them to you. If you qualify, you can join the study. If you do not join the study, we will still use some information collected about you (for example age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

First phase of the study

The study has three phases. If you join, you will start in the first phase. You will be given CAB and RPV pills to start taking. You will stop taking the other ARVs you were taking before.

You will have 3 study visits over 4-6 weeks (about one month). At these visits, we will:

- Collect information from your medical records.
- Ask questions about your health, ARVs, and other medications.
- Give you a physical exam.
- Collect blood for tests. This will be done using a needle in your arm.
- For girls, collect blood or urine for a pregnancy test.
- At the first visit, we may also do an ECG test of your heart.

Each visit will take about 1-3 hours.

Second phase of the study

At the fourth study visit, we will review all your test results to see if you qualify for the second phase of the study.

- If you do not qualify, you will stop taking CAB or RPV pills. You have one more visit about 4 weeks later. This visit will be like the other visits described above.
- If you qualify, you can enter the second phase of the study.

In the second phase of the study, you will have 25 study visits over about 2 years. The visits will be like the visits described above. At two of these visits, we will also look at your genitals again to see how developed you are.

You will not take CAB and RPV pills. Instead, you will be given shots of CAB and RPV. The shots will be given at 23 of the study visits (4 weeks apart, about once per month). You will get one shot of CAB and one shot of RPV each time. The shots will be in the buttocks (bottom, “cheeks”). The shots may be given on the same side of the buttocks or on different sides.

You may also be contacted to answer questions over the phone about how you feel about the shots.

After you finish the study visits in Cohort 2, you can decide to keep getting shots of CAB and RPV. If you decide not to keep getting shots of CAB and RPV, or if you stop the shots early, you will enter the third phase, which is also called the long-term follow-up phase of the study. This phase is described below.
Long-term follow-up safety phase of the study

You will have 4 or 5 study visits over 48 weeks (about 1 year). The visits will be like the visits described above. You will not be given CAB and RPV pills or shots. You will go back to taking your other ARVs.

Risks of the study

Having blood collected may cause pain, bleeding, bruising, swelling, or infection where the needle goes in your arm.

Having shots of CAB or RPV may cause pain, irritation, redness, bumps, swelling, itching, or bruising on the buttocks (where the shot is given). When CAB and RPV are given as shots, they stay in the body for much longer than when CAB and RPV are taken as pills.

CAB and RPV can cause other side effects. These side effects are common, but not everyone will have them. You may have pain, feel sick to your stomach, or vomit (throw up). You may have diarrhea. You may have a headache, fever, runny nose, sore throat, dry mouth, or rash. You may have trouble sleeping or a lack of energy. You may not want to eat as much as you usually do. You may feel light headed or sad. You may have problems in other parts of the body, such as your liver.

We do not yet know if CAB or RPV are safe in pregnancy. Early results from one study showed that the ARV called dolutegravir (DTG) may increase the risk of serious birth defects in the new baby. These mothers were taking the drug before they knew they were pregnant. The birth defects have not been seen when mothers started taking DTG later in pregnancy. CAB is not the same drug as DTG. We do not know if CAB can cause the same defects in babies.

Girls who are able to become pregnant must agree to use certain methods of birth control to be in this study. If you become pregnant during the study, please let us know right away.

We will check for side effects at each study visit. Please tell us if you have any side effects or don’t feel well. There is also a risk that the CAB and RPV pills and shots won’t control the HIV as well as the ARVs you were taking before. We will check the amount of HIV in your blood at each study visit. If you have side effects, or if the amount of HIV in your blood is higher than expected, you may have extra visits. We will talk with you and your parent/guardian about this, and tell you what to do about any side effects. We will also tell you if you can keep taking CAB and RPV. In some cases, you may have to stop taking CAB and RPV.

All information collected for this study will be kept private and confidential. However, it is possible that information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stressed or embarrassed.

Other information about the study

Study records may be reviewed by study staff and groups that oversee the study. Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- The United States National Institutes of Health and its study monitors
The United States Food and Drug Administration
The United States Office for Human Research Protections
Other U.S., local, and international regulatory entities
The IMPAACT Network that is coordinating the study
ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

[Sites may modify this paragraph to reflect local reporting requirements and legal statues: Your study information may be shared with other authorities if required by law. Public health authorities are required by law to receive information for the prevention or control of disease, injury or disability. (We must follow laws requiring the reporting of suspected child abuse and neglect).]

**Benefits of the study**

By joining the study, you will be part of the search for new ARVs for adolescents. The information learned in this study could someday lead to better ARVs for adolescents. However, being in this study may not be of any benefit to you.

**Your rights**

Taking part in this study is voluntary. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on the medical care you normally receive.

**Who to contact**

If you have questions about the study:
[insert name and telephone number of investigator or other study staff]

If you have questions about your rights or how you are treated in the study:
[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

If you have problems related to being in the study:
[insert name and telephone number of investigator or other study staff]

If you want to leave the study:
[insert name and telephone number of investigator or other study staff]

**Signatures**

*If you want to take part in this study, sign or make your mark below.*
Before deciding whether to take part in this study, make sure you have read this form, or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to take part.

We will tell you and your parent/guardian any new information that may affect your willingness to stay in the study. You can ask questions or ask for more information at any time.

You do not give up any rights by signing this form.

[Insert signature blocks as required by site IRB/EC policies.]

Name of Participant (print)  Signature of Participant  Date

Name of Study Staff Conducting Assent Process Name (print)  Signature of Study Staff  Date

Name of Witness  (as appropriate; print)  Signature of Witness  Date
Appendix IV-C: Sample Assent Form for Specimen Storage and Future Use for Participants who cannot provide independent informed consent

IMPAACT 2017

Version 2.0, dated 16 August 2018

[Throughout this form sites may modify to remove mentions of HIV and ARVs for participants who do not know their status].

Introduction

As part of the study, you will have blood and urine collected. After these samples are tested for the study, some samples may be left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

You are being asked for permission to keep your extra samples and use them for other research in the future. Your parent/guardian will also be asked for permission.

This form gives information about extra samples. Please read it, or have it read to you, and ask any questions you may have. After we talk about the information with you, you will record your decisions at the end of the form.

What happens with extra samples

If you allow your extra samples to be kept, there is no limit on how long they will be kept.

The samples may be used for research on HIV, the immune system, and other diseases.

If you agree, the samples could be used for research that looks at your genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people’s genes can help explain why some people get a disease while others do not. Your samples would only be used to look at genes related to HIV and the immune system.

The results of tests done with your samples will not be given to you or your parent/guardian.

Risks and benefits

When extra samples are kept for research, they are labeled with a code number only. No names are used. Therefore, there is very little risk to your privacy.

By allowing extra samples to be used for research, you will be part of the search for new information that may benefit people with HIV in the future. However, the research done with extra samples is not expected to be of benefit to you.

Information from research using extra samples may be reviewed by groups that oversee the research

These groups include:
• The IMPAACT Network
• The ethics committees that review and approve the research
• Government and other agencies that pay for the research
• Government and other agencies that monitor the research
• Other local, US, or international regulatory entities

The people who do research with the extra samples and the groups listed above are required to make efforts to
keep information private and confidential.

The results of research done with the extra samples may be presented publicly or published. However, no
presentation or publication will use your name or identify you personally.

Your rights

It is up to you and your parent/guardian to decide if your extra samples can be used for research. You can say yes
or no. If you say yes now, you can change your mind later. Your decision will have no effect on your participation
in the study. If you say no, all extra samples will be destroyed.

Who to contact

If you have questions about use of your extra samples:

[insert name and telephone number of investigator or other study staff].

If you change your mind about use of your extra samples:

[insert name and telephone number of investigator or other study staff].

If you have questions about your rights or how you are treated in the study:

[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

Signatures

Before deciding whether to allow your extra samples to be used for research, make sure you have read this form
or had it read to you. Make sure all your questions have been answered. You should feel that you understand your
choices and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies. Separate consent decisions must be
documented for genetic testing].

Please write your initials or make your mark next to your choices:

__________ I allow my extra samples to be used for research on HIV, the immune system, and other diseases.

__________ I allow my extra samples to be used for tests of my genes.

__________ I do not allow my extra samples to be used for any research.
<table>
<thead>
<tr>
<th>Name of Participant (print)</th>
<th>Signature of Participant</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Study Staff Conducting Assent Process Name (print)</td>
<td>Signature of Study Staff</td>
<td>Date</td>
</tr>
<tr>
<td>Name of Witness (as appropriate; print)</td>
<td>Signature of Witness</td>
<td>Date</td>
</tr>
</tbody>
</table>
Appendix V: Parent/Caregiver Participation in Qualitative Phone Interviews

Appendix V-A: Parent/Caregiver Qualitative Phone Interviews

Parents or caregivers of adolescent participants will be selected, by the protocol interview team, for enrollment into the study to conduct a single in-depth qualitative phone interview, with the purpose of evaluating their perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA. The phone interviews with parents/caregivers will be conducted separately and apart from any phone interviews conducted with adolescent participants.

The protocol interview team will notify sites to initiate recruitment of the selected parent/caregiver. After obtaining consent, sites will confirm eligibility for the parent/caregiver to take part in the interview. Parents/caregivers meeting eligibility criteria will be enrolled as study participants, and site staff will work with the protocol interview team and the enrolled parent/caregiver to schedule and conduct the phone interview. Further details relating to these processes and procedures are provided below.

Protocol Section 11 provides information and details regarding the qualitative phone interviews with the adolescent participants.

1 Sample Size, and Selection Process

Enrolled adolescent participants will be selected by the protocol interview team for their parent/caregiver to be recruited by site staff to take part in a single in-depth qualitative interview for a maximum of 60 completed phone interviews: 30 phone interviews completed by parents/caregivers of Cohort 1 adolescent participants, and 30 phone interviews completed by parents/caregivers of Cohort 2 adolescent participants. The sample size is based on the likely number of interviews needed to achieve thematic saturation. Parent/caregiver selection for the interviews will continue until there is either saturation of themes among the parent/caregiver interview data, or the parent/caregiver maximum sample size is reached. See Protocol Section 11.6 regarding thematic saturation and qualitative interview data analyses.

Parent/caregiver selection is based on the adolescent participant’s reported demographics from the adolescent’s Screening and Entry visits, with the goal of balancing interviewed parents/caregivers across female/male and older/younger adolescent participants. Additionally, parents/caregivers of participants who permanently discontinue injectable study product will be purposefully selected. This will ensure that perspectives from parents/caregivers across the range of enrolled participants are reflected in the final analysis. Parents/caregivers will be selected across multiple sites, but restricted to those willing and able to conduct the interview in English.

When possible, parents/caregivers of adolescents also participating in interviews will be selected to allow for dyadic comparisons between the parents’/caregivers’ and adolescents’ perspectives. However, a parent/caregiver of an adolescent participant may be selected to take part in the qualitative phone interview even if their adolescent participant is not selected or does not complete a (separate) qualitative phone interview.

The interviews must be completed within the applicable specified interview window (see Appendix V-A Section 2 below). Parents/caregivers will be selected on an on-going basis, and as their adolescent participant approaches the parent/caregiver interview procedural window. Parents/caregivers of adolescent participants enrolling to the study early will be selected for interviews first, as their adolescent participant will be the first to receive the injectable study products. The selection process will continue until thematic saturation or the sample size is reached for each Cohort; therefore, some parents/caregivers...
may be selected after entering the interview procedure window. Parents/caregivers who complete an interview for Cohort 1 will not be eligible to complete an interview for Cohort 2.

2 Phone Interview Procedural Windows

The qualitative phone interviews will be conducted with selected parents/caregivers of adolescent participants within the following timeframes:

- Parents/caregivers of Cohort 1 adolescent participants: Between the adolescent participant’s Week 4b and Week 12 visits (inclusive), or during LSFU visits.

- Parents/caregivers of Cohort 2 adolescent participants: Between the adolescent participant’s Week 24 and Week 96 visits (inclusive), or during LSFU visits.

3 Recruitment Considerations

The protocol interview team will notify sites of an adolescent participant’s PID to then initiate the recruitment of the adolescent participant’s parent/caregiver. Recruitment of the parent/caregiver will generally rely on the enrolled adolescent participant identifying the potentially eligible parent/caregiver and referring him/her to site staff for the qualitative interview; site staff may also identify a potentially eligible parent/caregiver (of the selected adolescent participant) as they present to the study clinic.

Sites must source document notification by the protocol interview team of adolescent participant selection for parent/caregiver recruitment, all attempts to contact the adolescent participant for parent/caregiver recruitment. Sites must follow their IRB/EC approved recruitment methods for approaching a potential parent/caregiver participant. Further guidance on recruitment considerations and processes is provided in the IMPAACT 2017 MOP.

Eligibility criteria for parents/caregivers are provided in Protocol Section 4.5, and details regarding confirmation of eligibility criteria and the enrollment process are provided in Appendix V-A Section 5.

4 Consenting Considerations

Parents/caregivers must provide consent prior to enrollment and conducting the phone interview. After recruitment of a selected and potentially eligible parent/caregiver, study staff will provide information, education, and counseling as part of the study informed consent process for the qualitative phone interview. The consent process will include information exchange, discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. Study staff will also provide time to address any questions or concerns the parent/caregiver may have, and an assessment of understanding, before proceeding to a consenting decision.

Obtaining informed consent from the parent/caregiver for the phone interview is ideally conducted in person and in writing by the parent/caregiver signing the informed consent form. Appendix V-B provides a sample written informed consent form for parent/caregiver study participation in the qualitative phone interview which sites may modify for use. If the parent/caregiver is unable to read, the process for consenting illiterate participants, as defined or approved by the local IRB/EC, should be followed.

Sites have the option of seeking a waiver from their IRB/EC of the requirement to obtain written documentation of the consent process for parent/caregiver participation in the qualitative phone interview. Consistent with DAIDS policies on the requirements for obtaining informed consent
When the IRB/EC considers waiving the requirement to obtain written documentation of the consent process, the IRB/EC reviews a written description of the information that will be provided, either verbally or in writing, to the parents/caregivers. Appendix V-C provides a sample of a script or statement which sites may modify for use, should an IRB/EC grant a waiver of written documentation.

Additionally, sites also have the option of seeking IRB/EC approval for obtaining parent/caregiver consent by telephone, rather than in person. In such instances, a witness to the consent process (e.g., another study or non-study staff member) must be present at the time of the study site staff obtaining consent from the parent/caregiver, and should ideally also listen in to the consenting discussion between the parent/caregiver and study staff member. Appendix V-C may be modified for use as a verbal script to obtain consent by telephone. If telephone consent is used and the parent/caregiver is seen at the site prior to conducting the phone interview, it is recommended to re-confirm the parent/caregiver’s understanding of the phone interview and willingness to participate through an additional, brief consent process, as required by the IRB.

Study sites are permitted to develop a separate parent/caregiver consent form and/or script for this study, if required by site or IRB/EC policies and procedures. Sites must establish and maintain an informed consent SOP with written procedures describing standards for obtaining informed consent, and roles and responsibilities of study staff involved in obtaining informed consent for all the consenting options being utilized for the parents/caregivers (i.e., written signed consent, waiver of written consent, and/or verbal consent by telephone), reflective of applicable IRB/EC guidance. For sites seeking IRB/EC approval for obtaining consent by telephone, the site’s informed consent SOP should include procedures for subsequently obtaining a written signed consent form from the parent/caregiver (unless the IRB waives written consent), and how a copy of the consent form (or script) will be provided to the parent/caregiver.

Regardless of a waiver of written consent, all the informed consent processes will be fully source documented, consistent with the DAIDS policies referenced in Protocol Section 12.2.

5 Eligibility Confirmation and Enrollment Process

Eligibility criteria for parents/caregivers are provided in Protocol Section 4.5. Inclusion criteria include confirmation from both the parent/caregiver as well as the adolescent participant that the identified parent/caregiver has knowledge of how the adolescent participant tolerated the study product, and lives with or has regular supportive contact with the adolescent participant. As these inclusion criteria require reporting from separate individuals, parent/caregiver eligibility may be assessed at multiple timepoints after obtaining consent and prior to enrollment, and may be assessed in-person at the study clinic or by telephone. It is generally expected that site staff will ascertain adolescent participant report of parent/caregiver eligibility during the adolescent’s study visit. Eligibility criteria must be confirmed and source documented after obtaining informed consent.

Eligibility determination for parents/caregivers must also be included in site SOPs, which describe how (whether in-person or over the phone), where and when recruitment and confirmation of eligibility criteria will be performed; roles and responsibilities for assessing (whether in-person or over the phone) and confirming eligibility; and procedures for documenting the process.

The DMC system will not be used for tracking parent/caregiver screening process. However, sites will source document reasons for any consenting parent/caregiver found to be ineligible. For parents/caregivers found to be eligible, enrollment into the study will occur upon successful entry of required eligibility data into the IMPAACT Data Management Center (DMC) Subject Enrollment System (SES). Successful entry into the SES will generate a study identification number (SID).
The IMPAACT 2017 MOP provides further guidance on operational and logistical considerations of assessing and confirming eligibility, and enrolling the parent/caregiver to the study prior to the phone interview being conducted.

6 Scheduling and Conducting Phone Interviews

Site staff will work with the protocol interview team and the parent/caregiver to schedule the phone interview at a time that is convenient for the parent/caregiver and within the applicable interview procedural window. Scheduling of the interview may occur at any point with the intention to minimize the number of scheduled but uncompleted interviews. Parents/caregivers must be consented, confirmed as eligible, and enrolled prior to conducting the phone interview.

Once the phone interview is scheduled, site staff will provide the parent/caregiver with detailed instructions and guidance on accessing the phone interview platform. Phone interviews may be completed either in the study clinic during their adolescent participant’s scheduled study visit, or from a phone outside the study clinic. All phone interviews will be conducted by a protocol interview team member external to participating clinical research sites, following an interview guide, and will be audio recorded and transcribed.

After obtaining consent, sites must source document all attempts to contact the parent/caregiver and interview scheduling attempts, and enter into eCRFs demographics and the date the phone interview occurred. Operational and logistical details regarding communication with the protocol interview team members and site staff are provided in the IMPAACT 2017 MOP.

7 Human Subjects Protections

Protocol Section 14.1 provides information regarding IRB/EC review and approval requirements in relation to the IMPAACT 2017 study. Informed consent considerations are provided in Appendix V-A Section 4 above.

There may be no direct benefit to parents/caregivers who take part in the qualitative phone interviews. Information learned in this study may be of benefit to adolescent participants and others in the future, particularly information that may lead to more treatment options for HIV-infected children and adolescents. Parents/caregivers may also appreciate the opportunity for themselves to contribute to HIV-related research.

Despite all efforts to maintain confidentiality, involvement in the qualitative phone interview could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because adolescent participants could become known as having HIV). For example, adolescent participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities.

Pending IRB/EC approval, parents/caregivers may be reimbursed for their time and any costs associated with completing the qualitative phone interview. Reimbursement amounts will be specified in the sitespecific consent, verbal script, or other materials if applicable per IRC/EC policies and procedures.

All study procedures will be conducted in private and every effort will be made to protect parent/caregiver privacy and confidentiality to the extent possible. Parent/caregiver information will not be released without written permission to do so except as necessary for review, monitoring, and/or
auditing as described in Protocol Section 13. Refer to Protocol Section 14.7 for further information on privacy and confidentiality.

8 Disclosure of Harm

As described above, the purpose of conducting in-depth qualitative phone interviews with parents/caregivers is to evaluate their perceptions of adolescent acceptability and tolerability of CAB LA and/or RPV LA. Conducting the interviews is not expected to increase the likelihood or risk of self-harm or harm to others.

During the consent process, parents/caregivers will be informed that the information they provide in the interview will be kept confidential, with the exception of disclosures of significant risk for harm, including suicidality, or at risk of committing harm toward others, including abuse, violence or homicidality.

If at any time during a qualitative phone interview, a parent/caregiver divulges that s/he is at significant risk for harm or at significant risk of committing harm toward the adolescent participant, or if harm is suspected or likely, or if the parent/caregiver states s/he is suicidal or homicidal, the following will occur:

- The protocol interview team member conducting the interview will immediately contact the site IoR or designee and share any time-sensitive, potentially life-threatening information received from the parent/caregiver as part of the phone interview discussions.
- The IoR or designee contacted with this information will follow local policies for management of such situations including engaging immediate/first responders as applicable.
- The IoR or designee will also follow local reporting policies and legal statutes, including reporting to child protection or other appropriate agencies, as well as arranging referrals to appropriate support, counseling or treatment resources.

For disclosure of safety concerns to the parent/caregiver, the IoR or designee will notify the CMC after completing the steps above. No further safety reporting of the parents/caregivers is required, and Protocol Section 7 Safety Assessment, Monitoring, and Reporting does not apply for the parents/caregivers.

For disclosure by the parent/caregiver of safety concerns to the adolescent participant, the IoR or designee will notify the CMC after completing the steps above, and document and report the event as applicable per Protocol Section 7.

To facilitate rapid communications, the IoR or designee is expected to provide up-to-date contact information to the protocol interview team while phone interviews are being scheduled and conducted with participants from the site.

9 Data Management, Clinical Site Monitoring, and Administrative Procedures

Protocol Section 11.6 provides details on the qualitative phone interview data analyses, and Protocol Section 12 provides details on the management, handling, and record keeping of the qualitative phone interview data. Protocol Section 13 provides information on clinical site monitoring, and Protocol Section 15 provides information on overarching administrative procedures for the IMPAACT 2017 study.
Appendix V-B: Parent/Caregiver Phone Interview Sample Informed Consent Form
for parents/caregivers of adolescents enrolled in:

IMPAACT 2017
Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectible Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV-Infected Children and Adolescents

Version 2.0, dated 16 August 2018

Introduction

You are being asked to take part in the research study named above.

This form gives information about your role in the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand your role in the study. At the end, we will ask you questions to see if we have explained your role in the study clearly.

After you understand your role in the study, and if you decide that you will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

It is your decision whether or not you join the study.

Deciding to join the study is voluntary. You may choose to join or not join. If you choose to join, you can change your mind and stop the study at any time. Your choice will have no effect on your child’s medical care at this clinic or your child participating in the study. Access to services and the benefits and rights you and your child normally have will not be affected.

Your role in the study

If you agree, you may be asked to complete one phone interview about how you felt and how you think your child felt about the shots they receive in this study. Not all parents/caregivers of adolescents who receive shots will be asked to complete a phone interview. Some, but not all adolescents who receive shots will also be asked to complete a phone interview.

If you are eligible and selected to complete an interview, we will help you to schedule the interview at a time that works for you. During the interview, you will be asked questions about how you felt about your child receiving shots of CAB or [and] RPV. The interview will be audio recorded. The words that you say will then be written down. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about them receiving the shots.

The interview may take place at or in between your child’s the Week 4b, 5, 6, 8, and 12 study visits [Week 24 through 96 visits], in Cohort 1 [Cohort 2] or during the long-term follow-up visits . The interview could also take place at or in between any of the long-term follow-up visits if your child enters into long-term follow-up. You will only complete one interview. Your part in the study should take about 1-2 hours.

There are no costs from being in the study.
There are no costs to you for this phone interview.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for your time, and given (specify amount).]

**Possible Risks**

There could be risks of disclosure of your information. We will make every effort to keep your information private and confidential. Your and your child’s names will not be included in the recording of the interview. The interview will only be labeled with a code number.

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

**Possible Benefits**

By joining the study, you will be part of the search for ARVs that may be better for adolescents. There may be no direct benefit to you from taking part in this study. There may be a benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. Information learned from this study may help other adolescents who have HIV.

**Other information about the study**

Study records may be reviewed by study staff and groups that oversee the study. Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child’s name or identify your child personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.
Sites may modify this paragraph to reflect local reporting requirements and legal statues: Your child’s study information may be disclosed to other authorities if required by law. Public health authorities are required by law to receive information for the prevention or control of disease, injury or disability. (We must comply with laws requiring the reporting of suspected child abuse and neglect.)

**Signatures**

*If you agree to participate in this study, please sign or make your mark below.*

Before deciding whether to participate in this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to join. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

*Insert signature blocks as required by site IRB/EC policies.*

**Signature blocks for participants of legal age to provide independent informed consent**

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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<tr>
<th>Study Staff Conducting Consent Discussion (print)</th>
<th>Study Staff Signature and Date</th>
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<tr>
<th>Witness’s Name (print) (As appropriate)</th>
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Appendix V-C: Parent/Caregiver Phone Interview Sample Informed Consent Verbal Script
for parents/caregivers of adolescents enrolled in:

IMPAACT 2017

Version 2.0, dated 16 August 2018

Introduction

You are being asked to take part in the research study named above.

This form gives information about your role in the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand your role in the study. At the end, we will ask you questions to see if we have explained your role in the study clearly.

After you understand your role in the study, and if you decide that you will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

It is your decision whether or not you join the study.

Deciding to join the study is voluntary. You may choose to join or not join. If you choose to join, you can change your mind and stop the study at any time. Your choice will have no effect on your child’s medical care at this clinic or your child participating in the study. Access to services and the benefits and rights you and your child normally have will not be affected.

Your role in the study

If you agree, you may be asked to complete one phone interview about how you felt and how you think your child felt about the shots they receive in this study. Not all parents/caregivers of adolescents who receive shots will be asked to complete a phone interview. Some, but not all adolescents who receive shots will also be asked to complete a phone interview.

If you are eligible and selected to complete an interview, we will help you to schedule the interview at a time that works for you. During the interview, you will be asked questions about how you felt about your child receiving shots of CAB or [and] RPV. The interview will be audio recorded. The words that you say will then be written down. This information will help us understand if CAB shots and RPV shots have any bad side effects for adolescents. It will also help us understand how adolescents and families feel about them receiving the shots.

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There are no costs from being in the study.
There are no costs to you for this phone interview.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for your time, and given (specify amount).]

Possible Risks

There could be risks of disclosure of your information. We will make every effort to keep your information private and confidential. Your and your child’s names will not be included in the recording of the interview. The interview will only be labeled with a code number.

To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.

Possible Benefits

By joining the study, you will be part of the search for ARVs that may be better for adolescents. There may be no direct benefit to you from taking part in this study. There may be a benefit if the results from this study lead to a safe and effective dose of the study drugs for adolescents. Information learned from this study may help other adolescents who have HIV.

Other information about the study

Study records may be reviewed by study staff and groups that oversee the study. Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site drug regulatory authority]
- [insert name of other site regulatory entities]
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- ViiV Healthcare (the company that makes CAB)

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child’s name or identify your child personally.

A description of this study will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.
[Sites may modify this paragraph to reflect local reporting requirements and legal statues: Your child’s study information may be disclosed to other authorities if required by law. Public health authorities are required by law to receive information for the prevention or control of disease, injury or disability. (We must comply with laws requiring the reporting of suspected child abuse and neglect).]

Agreement to participate

Before deciding whether to participate in this study, please ask me any questions that you have. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to join. You are welcome to ask questions or request more information at any time.

You do not give up any rights by agreeing to participate.

[Insert signature blocks as required by site IRB/EC policies.]

Signature blocks for witnesses to verbal consent of parents/guardians of legal age to provide independent informed consent

Participant’s Name (print)          Participant’s Signature and Date

Study Staff Conducting Consent Discussion (print)   Study Staff Signature and Date

Witness’s Name (print) (As appropriate)   Witness’s Signature and Date