Summary of Changes Included in the Full Protocol Amendment of:

IMPAACT 2017

“MOCHA”
More Options for Children and Adolescents

The Amended Protocol is Identified as:

Version 3.0, Dated 13 August 2020

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

Table of Contents

Information/Instructions to Study Sites from the Division of AIDS .............................. 1
Summary of Modifications and Rationale ........................................................................ 2
Implementation ........................................................................................................... 6

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the IMPAACT 2017 study, including the study informed consent and assent forms (ICFs), 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 site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

For sites currently implementing the study, after obtaining IRB/EC approval and any other applicable regulatory entity approvals, each site must receive IMPAACT 2017 protocol team approval prior to implementing this amendment and using the updated ICFs. After implementation approval is obtained, the updated ICFs are to be used for all new participants. In addition, after IMPAACT 2017 protocol team implementation approval is obtained, all previously enrolled participants still on-study must be re-consented at their next study visit using the updated ICFs, unless otherwise directed by the IRB/EC. Re-consenting is not required for specimen storage and future use, unless otherwise directed by site IRB/EC. Sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the amendment after the DAIDS PRO verifies that all required registration documents have been received and are complete. Approval from the DAIDS PRO is not required prior to implementing the amendment.
For sites not yet implementing the study, all required approvals of this amendment must be obtained before initiating this study. Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the amendment after the DAIDS PRO verifies that all required registration documents have been received and are complete. This notification must be received before implementation of this amendment. Receipt of this notification will be confirmed as part of the site-specific study activation process for this study.

This Summary of Changes, Version 3.0 of the protocol, corresponding site-specific ICFs, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO should be retained in each site’s essential document files for IMPAACT 2017.

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**Summary of Modifications and Rationale**

The main purpose of this amendment is to modify the injectable dosing regimen for Cohort 2 Step 4 participants from receiving study product injections every four weeks (Q4W) to every eight weeks (Q8W), and for Cohort 1 Step 2 participants from receiving three study product injections per the Q4W dosing regimen to receiving two study product injections four weeks apart (which aligns with the initiation of the Q8W dosing regimen). This amendment will also reduce the Cohort 1C target sample size in response to ViiV Healthcare, Inc.’s request to the FDA to modify the Pediatric Investigation Plan (PIP), clarify the definition of “evaluable participant” for safety and virologic analysis purposes separately from dose-finding purposes, and define interim analysis #2 specifying the timing and criteria for opening Cohort 2 to participants who have not previously enrolled to Cohort 1. Other modifications include added results from the adult studies and added language throughout the protocol allowing study implementation (except for the qualitative phone interview component) in Botswana, South Africa, Thailand, and Uganda.

The protocol and informed consents and assent forms have been modified with language regarding potential risks from receiving the injection, relevant updates to the Investigator Brochures for all study products, information about the FDA action regarding the injectable study products, current requirements of the Common Rule (per United States Code of Federal Regulations 45 CFR 46), visit schedule and study procedure revisions regarding the study product dosing regimen changes, and other formatting changes to improve readability. This amendment incorporates clarifications from and updates some of the content provided in Clarification Memoranda (CM) #1 and #2, and Letter of Amendment (LoA) #1 issued under protocol Version 2.0. Other modifications, clarifications and administrative edits are also incorporated to improve readability and consistency across protocol sections.

Modifications incorporated into the protocol are summarized as follows:

- The dosing regimen for the injectable study products in both Cohorts 1 and 2 have been modified from injections every 4 weeks to injections every 8 weeks. For both Cohorts, the first two injections (occurring during the Week 4b and Week 8 visits) remain four weeks apart, per the dosing regimen in the adult studies. Language throughout the introduction section has been updated to reflect this change and to provide the rationale, including incorporating results from the adult studies as well as an overview of preliminary data from IMPAACT 2017, with less relevant language in the introduction section consolidated or removed. Updates reflecting this change have also been incorporated into the study design, study product, procedural sections (for Cohort 1 and 2, and long-term safety and washout PK follow-up (LSFU), as well as to the
statistical and clinical pharmacology sections; and related updates to the PK models were incorporated in the clinical pharmacology section.

- Information has been added to further define evaluable participants for safety and PK analyses, with a separate definition of dose-evaluable for the purposes of the dose-finding algorithm. The dose-evaluable definition applies to the Cohort 1 target sample sizes, which have also been updated to specify “dose-evaluable.” The definition of safety evaluable in the statistical considerations section has been modified so that participants experiencing virologic failure are not considered safety-failures, consistent with other dose-finding Phase I/II studies.

- On 20 December 2019, the FDA deferred approval CAB LA and RPV LA for the treatment of HIV-1 infection in adults due to the Chemistry, Manufacturing and Controls data that were presented to the FDA for both products. ViiV Healthcare will provide the FDA with additional requested Chemistry, Manufacturing and Controls information so that the FDA may complete their review. Information about this FDA action has been added to the sample informed consent and assent forms.

- A secondary objective was added for Cohort 1 to monitor viral suppression through Week 16. Secondary outcome measures were updated accordingly.

- The Cohort 1C target sample size has been reduced from approximately 20 evaluable participants to approximately 15-20 dose-evaluable participants, reflective of ViiV Healthcare’s request to the FDA to modify the Pediatric Investigation Plan (PIP). The overall target sample size for Cohort 1 has also been reduced from approximately 35 evaluable to approximately 30 to 35 dose-evaluable, to reflect the reduction of the Cohort 1C target sample size.

- Language to further clarify the study analyses has been incorporated throughout the protocol. The introduction, study design, and statistical considerations sections have been updated to specify that interim analysis #1 was conducted under protocol Version 2.0, and to clarify that the purpose of interim analysis #1 is to establish the dose of the oral and injectable CAB study products, and the injectable RPV study product to be provided in Cohort 2. Interim analysis #2 has been added to define and specify the timing and criteria for opening Cohort 2 to study-naive participants. Once approximately 15-20 Cohort 1C participants and approximately 15 Cohort 1R participants contributing to the dose-finding algorithm have enrolled, and 80% of these participants have completed the Step 2 Week 8 visit, interim analysis #2 of safety and PK evaluations will be performed (followed by a SMC review) 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. The Cohort 1 final analysis has also been clarified.

- Select eligibility criteria have been clarified. Inclusion criterion 4.1.6 has been modified for consistency with updated standard IMPAACT Network language. Inclusion criterion 4.1.7 has been updated to require participants have at least 3 consecutive months on a stable cART regimen and clarifies the definition of a stable cART regimen. Inclusion criterion 4.1.8 and 4.1.9 have been combined and updated for consistency with the adult studies regarding timeframes for required documentation of HIV-1 RNA results. Inclusion criterion 4.1.10 has been updated to also apply to participants enrolling to Cohort 2 Step 3. Inclusion criterion 4.1.13 has been updated for clarity and to reinforce the ECG requirements of the protocol. Inclusion criterion 4.1.16 has been modified to require completion of Cohort 1 Step 2 injections and the Week 16 visit for Cohort 1 participants enrolling to Cohort 2; an exception to this criterion was added to allow for extenuating circumstances including COVID-19 site disruptions. Exclusion Criterion 4.2.1 has
been updated for consistency with the adult and other IMPAACT studies for the time points regarding timeframes for required documentation of HIV-1 RNA results and specifying that the lower limit of detection for the assay be referenced. 4.2.2 was expanded to cover (i.e. exclude from enrollment to Cohort 2 Step 3) any Cohort 1 participant who has been permanently discontinued from study treatment due to study product-related toxicities (regardless of grade) during participation in Cohort 1.

- The introduction, study product, human subjects protections, and informed consents and assents have been revised with relevant updates from the Investigator Brochures for all study products.

- The study product and procedural sections have been updated to allow study implementation at non-US sites.

- Study guidelines related to oral and long-acting study products were clarified throughout the protocol in the study product, study procedures, and participant management sections. During Cohort 1 Step 1 and Cohort 2 Step 3 the number of oral study product doses was clarified to be a maximum of 43 doses. Clarification of when the last oral study product dose should be administered (for Cohort 1 Step 1 and Cohort 2 Step 3) was added to the protocol, as well as guidance on when to stop participant background cART regimen prior to initiating the oral study product for Cohort 2 Step 3 participants. Details regarding implementation of short-term oral bridging and resuming study product injections following short-term oral bridging for Cohort 2 Step 4 participants, as well as information on resuming cART following permanent discontinuation of study products (Cohort 2) were also specified. The study design and study product sections have been updated to reinforce that participants on a non-boosted INSTI-based cART regimen will be assigned to Cohort 1R.

- Modifications to the study visit windows, injection visit spacing requirements, and additional study visit flexibility has been incorporated into the protocol. The procedural sections of the protocol have been updated to allow non-injection study visits to be conducted outside of the clinical research site (e.g. home visits), modify the minimum and maximum spacing requirements between study product injections, and remove allowable visit windows from study product injection visits. Additional information was included to clarify which visits may not be conducted as split visits.

- Modifications to specified study visits were incorporated throughout the protocol. For both Cohorts 1 and 2 resistance testing plasma collection was modified to whole blood collection at the Entry visit along with the Early Termination visit. For consistency with the adult studies, an ECG was added to the Week 4b visit for Cohort 2. To account for Q8W dosing several study visits have been removed in Cohorts 1 and 2. The number of PK collections has been reduced for the Cohort 1 Week 2 and Cohort 2 Week 2 PK visits.

- The timing of shipping PK samples and resistance samples was updated.

- The procedural sections clarified that a limited battery of acceptability and tolerability assessments will be conducted for non-English speaking and non-Spanish speaking participants.

- The Clinical Management Committee (CMC) member listing in the safety assessment, monitoring, and reporting section has been updated to include the Laboratory Center representative, at least one statistician from ViiV, at least one pharmacology representative from ViiV and at least one from Janssen, and to allow for a medical representative designee from ViiV.
and Janssen. This section has also been modified to include Grade 3 or higher ALT as a triggered notification to the CMC by site investigators.

- The management of QTC prolongation has been updated for clarity and consistency throughout the protocol.

- The management of abnormal total bilirubin test results has been clarified for direct bilirubin testing upon an abnormal total bilirubin test result, as well as to reinforce the requirement of a direct bilirubin test result to assess total hyperbilirubinemia as atazanavir-related.

- The safety reporting and statistical considerations sections have been updated to include life-threatening adverse events assessed as related to study products as Primary Endpoints and in the Primary Analysis.

- The qualitative phone interview, data handling and record keeping sections and Appendix V have been clarified that the qualitative phone interview component will only apply for participants enrolled at U.S. sites.

- The statistical considerations section has been updated to reflect the modifications to the Q8W dosing regimen, reduced sample size for Cohort 1C, definition of evaluable participant for analysis versus dose-finding, addition of interim analysis #2, and the clarification of secondary outcome measures regarding HIV-1 RNA, as described above. Scenarios describing safety-triggered study decisions, dose adjustment decisions, and analyses which are no longer applicable due to the preliminary study data described above, have been removed. Additionally, the statistical considerations section has been clarified that the CMC will make an assessment of the relationship of adverse events listed in toxicity summary reports to document site attribution concurrence or lack thereof. Language has been added that special statistical and data analysis considerations may be warranted due to COVID-19 impact on study data, and that further analyses may be conducted as necessary to support regulatory submissions and publications, with such analyses described in an analysis plan.

- The clinical pharmacology plan section has been updated to reflect the modifications to the Q8W dosing regimen, reduced sample size for Cohort 1C, and related updates to the PK models, as described above. The primary endpoints, outcome measures, and expected outcomes have also been updated to reflect the revised PK sampling schedule, the Q8W dosing regimen, preliminary study data and new adult data. This section has also been clarified that Cohort 1 samples will undergo ongoing routine analysis and reporting with scheduled interim PK analyses to assess if the initial dosing is achieving the PK targets.

- The schedules of evaluations (Appendices I-A, I-B, and I-C) have been updated to reflect the current visit schedules and evaluations per the dosing regimen change and other modifications described in this document.

- The sample informed consent and assent forms have been updated to reflect revised risk language related to vasovagal reaction as observed in the adult studies, and updates from the Investigator Brochures for all study products. Changes were also made to reflect current requirements of the Common Rule (per United States Code of Federal Regulations 45 CFR 46), including the addition of a concise and focused presentation of key information to the beginning of each form, specification that the research will not include whole genome sequencing, and specification that information collected from this study may be used for other research in the future including
anonymized information about the consenting participant, visit schedule and study procedure revisions regarding the Q8W dosing regimen, formatting changes to improve readability, and to reflect other protocol modifications as described in this document.

- Appendix VI *Injectable Study Product Preparation* was newly added to incorporate injectable study product preparation requirements into the protocol.

- Appendix VII *Operational Guidance for Sites Responding to COVID-19* was newly added to incorporate implementation guidance to safeguard the health and well-being of study participants and study staff in the context of circulating SARS-CoV-2 and the associated coronavirus disease 2019 (COVID-19).

- The protocol team and study site rosters have been updated to reflect current membership. References, table and figure numbering, section numbering, and internal section references have been updated and other administrative updates and corrections have been incorporated throughout the protocol for accuracy, consistency, and clarity. The table of contents has been updated to reflect current protocol sections and page numbers.

### Implementation

The changes in the protocol text and informed consent forms are summarized below, generally in order of first appearance in the protocol.

1. The amended protocol is identified as FINAL Version 3.0, dated 13 August 2020. The table of contents, abbreviation and acronym list, reference list, and protocol team and study site rosters have been updated. The protocol cover page has been modified to update the Clinical Trials Specialists. Other administrative updates and corrections have been incorporated throughout the protocol for accuracy, consistency, and clarity.

2. The schema has been updated with a reduction in the Cohort IC target sample size from approximately 20 evaluable participants to approximately 15 to 20 dose-evaluable participants. The Cohort I overall target sample size has also been reduced from a minimum of 35 evaluable participants to approximately 30 to 35 dose-evaluable participants. Internal references have been updated for the protocol sections describing the dose-evaluable and evaluable definitions. The following have also been affected by the Cohort IC and Cohort 1 target sample size revisions: Figure 1 in the Schema, Sections 3.1, 9.1, 9.4, and 9.5.

3. The schema has also been revised with references to the qualitative phone interview as only applying to participants enrolled at U.S. sites. The following have also been affected by this revision: Sections 3, 4.5, 11, 12, and Appendix V.

4. The schema has also been updated with the revised Q8W dosing regimen consistent with the revisions incorporated into protocol Sections 3, 5, 9 and 10. Additionally, reference to the potential of the Cohort 2 doses being adjusted based on experience in Cohort 1 has been removed from the schema, consistent with the revisions described in protocol Section 9.

5. The schema was also modified with updated expectations for accrual timelines.
6. A secondary objective for Cohort 1 was newly added to monitor maintenance of viral suppression through Week 16, and in the Other Objectives section “washout” was added to the description for the long-term safety and washout PK follow-up phase of the study. These changes were also incorporated into Sections 2.3.1, 2.5.4, and 2.5.5 respectively, and subsequent section numbering has been updated.

7. In the schema, Figures 1 through 4 were updated for consistency per modifications described in this document.

8. Section 1 has been updated with data from the adult studies (ATLAS, ATLAS-2M, FLAIR, LATTE, and LATTE-2), including Q8W dosing regimen data, and information from the Investigator’s Brochures for each study product. The following sub-sections have been affected by these changes: Section 1.1, 1.2, 1.3, 1.4.

9. Section 1 has also been updated with all previous Tables removed, and Tables 1-4 newly added. All Figures in Section 1 are also removed, except Figures 7-8b (added per Version 2.0, LoA #1) which have been renumbered as Figures 5, 6, and 7.

10. Section 1.3.1 Protocol Version History was newly added with clarification that Interim Analysis #1 was completed per protocol Version 2.0, using the definitions of evaluable participants as presented in that version, and clarification that participants enrolled to protocol Version 2.0 received the Q4W dosing regimen; subsequent section numbering has been updated.

11. Section 1.3.2 Preliminary Review of Study Data (added per Version 2.0, LoA #1) has been updated with additional preliminary study data providing justification and rationale for the dosing regimen change to Q8W injections.

12. Section 1.3.6 Rationale for Change in IM Dosing Regimen (from Q4W to Q8W) was newly added with text incorporated from LoA #1 (under Version 2.0) and subsequent section numbering updated.

13. Section 1.5 has been corrected with changing the references to the long-acting injections to “LA”, for consistency across protocol sections, and maintenance of viral suppression was added for the Cohort 2 hypothesis.

14. In Section 3, details regarding the Cohort 1 interim analyses have been removed and replaced with summary text, to reduce redundancies with Section 3.1 Cohort 1. The Cohort 1 final analysis has been clarified, and this clarification has also been incorporated into Section 3.1.

15. In Section 3.1 clarification has been added that participants on a “non-boosted” INSTI-based cART regimen will be assigned to Cohort 1R, to increase consistency with the prohibited medications. This section has also been updated for consistency with the Cohort 1 Week 2 PK sampling timepoint revisions, as described in protocol Section 6, and language clarified for consistency across protocol sections regarding when participants are expected to receive their last dose of oral study product during Step 1.

16. Section 3.1 has also been updated with the revised visit schedule per the Q8W dosing regimen consistent with the visit schedule revisions incorporated into protocol Section 6 and the Schedules of Evaluations.
17. Section 3.1 has also been updated with sub-headers added to label Interim Analysis #1 (with reference to this analysis having been completed under protocol Version 2.0), Interim Analysis #2, and Cohort 1 Final Analysis. The target sample for interim analysis #1 was updated to specify dose-evaluable participants and clarified purpose of the analysis to establish the dose for Cohort 2. Language was added specifying that interim analysis #2 will be conducted once approximately 15-20 Cohort 1C participants and approximately 15 Cohort 1R participants contributing to the dose-finding algorithm have enrolled, and 80% of these participants have completed the Step 2 Week 8 visit. Clarification was added to the Cohort 1 Final Analysis regarding the closing of Cohort 1 to accrual and the timing of performing the end of cohort analysis with all Cohort 1 data.

18. In Section 3.2, language was clarified for consistency across protocol sections regarding when participants are expected to receive their last dose of oral study product during Step 3. This section has also been updated with the revised visit schedule per the Q8W dosing regimen consistent with the visit schedule revisions incorporated into protocol Section 6 and the Schedules of Evaluations.

19. Section 3.2 was also updated with clarifications regarding continued access to the injectable study products external to the study, for Cohort 2 Step 4 participants, consistent with protocol Section 14.11.

20. Section 3.3 was updated with a revised long-term safety and washout PK follow-up (LSFU) visit schedule with the first LSFU visit occurring at LSFU Week 8, and the target visit date and target window were adjusted accordingly. Additionally, the LSFU Week 4 and LSFU Week 12 visits have been removed, and the first LSFU visit for Cohort 1 participants completing the Step 2 Week 16 visit has been specified as the LSFU Week 24 visit. This section was also updated to specify for Cohort 2 Step 3 participants to resume (non-study provided) cART within 4 weeks following permanent discontinuation of oral study products, and for Cohort 2 Step 4 participants to resume (non-study provided) cART at 8 weeks (±7 days) following permanent discontinuation of injectable study products. This section was also updated with clarification of which specific participants are followed per the LSFU visit schedule upon permanent discontinuation of study product, and that a sub-set of participants may complete the qualitative interviews during LSFU visits. These changes were also made to Section 6.5, with sub-section numbering updated.

21. The following inclusion criteria have been updated:
   a. Inclusion criterion 4.1.6 has been modified for consistency with updated IMPAACT Network standards on the documentation requirements for confirmation of HIV-1 infection.
   b. Inclusion criterion 4.1.7 has been updated to require participants have at least 3 consecutive months on a stable cART regimen, clarifies the definition of stable cART regimen as unchanged, and incorporates revised language on determination of the criterion.
   c. Inclusion criteria 4.1.8 and 4.1.9 have been combined (and renumbered as 4.1.8) and updated for consistency with the adult studies regarding timeframes for required documentation of HIV-1 RNA results, and the reference point has been modified to be the lower limit of detection of the assay; subsequent inclusion criteria numbering has also been updated.
   d. Inclusion criterion 4.1.10 has been updated to require a total bilirubin value of ≤ 1.5 mg/dL, or normal direct bilirubin, at screening for participants on an atazanavir-containing (ATV) cART regimen enrolling to Cohort 2 Step 3.
   e. Inclusion criterion 4.1.12 has been updated for clarity and to reinforce the ECG requirements of the protocol.
   f. Inclusion criterion 4.1.13 has been updated to specify that either a blood or urine pregnancy test may be used.
g. Inclusion criterion 4.1.1 has been modified to require completion of Cohort 1 Step 2 study product injections as well as the Step 2 Week 16 visit for Cohort 1 participants enrolling to Cohort 2 and an exception to this criterion was added to allow for extenuating circumstances, including COVID-19 site disruptions.

22. Exclusion criterion 4.2.1 has been updated for consistency with the adult studies and other IMPAACT studies for the timeframes for required documentation of HIV-1 RNA results, and the reference point has been modified to be the lower limit of detection of the assay.

23. Exclusion criterion 4.2.2 was expanded cover (i.e. exclude from enrollment to Cohort 2 Step 3) any Cohort 1 participant who has been permanently discontinued from study treatment due to study product-related toxicities (regardless of grade) during participation in Cohort 1, as shown below.

24. Section 5.1 has been clarified that participants enrolled to Version 2.0 received the Q4W dosing regimen presented in that document.

25. Section 5.1.1 was updated with clarification that participants on a “non-boosted” INSTI-based cART regimen will be assigned to Cohort 1R, to increase consistency with the prohibited medications, and language clarified for consistency across protocol sections regarding when participants are expected to receive their last dose of oral study product during Step 1. Additionally, Table 5 has been updated to the Q8W study product injection dosing regimen for Cohort 1, and clarification that Step 1 participants may receive up to 43 doses of oral study product, as shown below.

26. Section 5.1.2 was updated with language clarified for consistency across protocol sections regarding when participants are expected to receive their last dose of oral study product during Step 3. Additionally, Table 6 has been updated to the Q8W study product injection dosing regimen for Cohort 2, and clarification that Step 3 participants may receive up to 43 doses of oral study product, as shown below.

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>IC</td>
<td>1</td>
<td>CAB administered orally as one 30 mg tablet once daily, beginning at the Entry visit, for 4-6 weeks (up to 43 doses), with or without food.</td>
</tr>
<tr>
<td></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), and at Week 8 (600 mg/3 mL).</td>
</tr>
<tr>
<td>IR</td>
<td>1</td>
<td>RPV administered orally as one 25 mg tablet once daily, beginning at the Entry visit, for 4-6 weeks (up to 43 doses), with a meal.</td>
</tr>
<tr>
<td></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), and at Week 8 (900 mg/3 mL).</td>
</tr>
</tbody>
</table>
Summary of Changes to IMPAACT 2017  
From Protocol Version 2.0 to Version 3.0  

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 (up to 43 doses of each).</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>First and second set of injections: 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) and at Week 8. Subsequent injections: starting at the Week 16 visit, CAB LA administered as a 600 mg (3 mL) IM injection in the gluteus medius muscle AND RPV LA administered as a 900 mg (3 mL) IM injection in the gluteus medius, every eight weeks through Week 96.</td>
</tr>
</tbody>
</table>

27. Section 5.1.4 header has been newly added to separate Short-term Oral Bridging for Cohort 2 Step 4 Participants from the previous sub-section, and the subsequent section numbering has been updated. This section has also been updated with clarification and additional detail regarding study product considerations for short-term oral bridging implementation, including references to interim injection visits consistent with the revisions incorporated into protocol Section 6.

28. Section 5.2 has been updated with additional and clarified descriptions of the study products.

29. Section 5.5 has been updated with instructions regarding final disposition of study product at non-US sites.

30. Section 6.1.1 has been modified with the removal of broader allowable visit windows for injection visits and updated minimum and maximum spacing requirements between study product injections, per the Q8W dosing regimen. Clarification was also added that, depending on when the previous injection was administered within the previous target visit window, the minimum and maximum spacing requirements may impact the availability of a target visit window (including the target visit date).

31. Section 6.1.2 has been clarified that visits may be split, with procedures performed on more than one day within the target visit window or allowable visit window (if applicable), and an interim visit may be conducted to dispense oral study products for Cohort 2 Step 4 participants requiring short-term oral bridging, consistent with the revisions incorporated into protocol Section 5.

32. Section 6.1.3 has been newly added providing that non-injection follow-up study visits or non-injection interim visits may be conducted at an off-site location, if allowed per local law and regulations and/or institutional policies.

33. Section 6.2 was updated with added instruction on when potential Cohort 2 Step 3 study participants should be counseled to stop their pre-study cART regimen. This clarification was also made to Section 6.4.1.

34. Section 6.3.1 was clarified that the Entry visit may not be conducted over a multi-day split visit, and that Cohort 1R participants should be provided a meal with their observed oral study product dose. Additionally, the stored sample for resistance testing was changed from plasma to whole blood. These clarifications and changes were also made to Section 6.4.1 (with all Cohort 2 participants provided with a meal with the observed oral study product dose).
35. Section 6.3.2 was updated with revised PK sampling timepoints at the Cohort 1 Step 1 Week 2 visit, including the removal of the 24-hour post-dose timepoint; references to the 24-hour post-dose timepoint have also been removed from this and other sections throughout the protocol. For Cohort 1C, the PK sampling timepoints have been revised to pre-dose, 1, 2, 3, 4, and 8 hours post-dose (6 PK collection timepoints); for Cohort 1R the PK sampling timepoints have been revised to pre-dose, 4, and 8 hours post-dose (3 PK collection timepoints).

36. Section 6.3.4 has been clarified for improved readability, and that the Cohort 1 Step 2 Week 4b visit may not be conducted over a multi-day split visit.

37. Sections 6.3.6 through 6.3.9 have been updated per a modified visit schedule as follows; these modifications have been incorporated into Appendix I-A, as appropriate:
   a. Study visits at Weeks 6, 13, and 14 have been removed and subsequent section numbering updated.
   b. The Week 9 study visit has been updated to be conducted at the clinical research site, acceptability/tolerability assessments removed, and an ECG and single PK sample have been added.
   c. The Week 12 study visit has been updated to be truncated, acceptability/tolerability assessments removed, laboratory evaluations have been reduced to a single PK sample timepoint, and the study product injection has been removed. The target date, visit window, and allowable window were adjusted.
   d. The target visit date for the Week 16 visit was updated.

38. Section 6.4.2, the Cohort 2 Step 3 Week 2 visit, was updated with the 2-7 hours post-dose PK sampling timepoint changed to occur at 3 hours post-dose (± 1-hour window). This modification is also described in Appendix II-B and III-B, as noted below in Summary of Changes item #111.

39. Section 6.4.4 has been clarified for improved readability, and that the Cohort 2 Step 4 Week 4b visit may not be conducted over a multi-day split visit; an ECG occurring 2 hours post-injection dose (with a ±1-hour window) was also added to this visit. This modification is also described in Appendix II-B and III-B, as noted below in Summary of Changes item #111.

40. Sections 6.4.6 through 6.4.13 have been updated per a modified visit schedule as follows; these modifications have been incorporated into Appendix I-B, as appropriate:
   a. Study visits at Weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, and 92 have been removed and subsequent section numbering updated.
   b. For the study visits at Weeks 32 and 40, a single PK sample has been added.
   c. For the Week 56 study visit, hematology and chemistry laboratory evaluations have been added.
   d. For the study visits at Weeks 64 and 80, hematology and chemistries, HIV-1 RNA, stored plasma for resistance testing, and PK sampling have been added.
   e. For the Week 72 study visit, HIV-1 RNA laboratory evaluation, stored plasma for resistance testing, and PK sampling have been removed.
   f. The Week 88 visit, hematology and chemistry and PK sampling have been added.
   g. The Week 96 visit was updated with clarifications regarding continued access to the injectable study products external to the study, for Cohort 2 Step 4 participants, consistent with protocol Section 14.11.

41. Section 6.4.14 was newly added to incorporate scheduling guidance and procedural requirements for an interim injection visit for Cohort 2 Step 4 participants resuming injections following short-term oral bridging. The generally expected guidelines for scheduling an interim injection visit, per
CMC consultation, have also been described. Appendix I-B has been updated to include a column depicting the interim injection visit evaluations, with footnote #7 newly added to refer to Section 6.4.14.

42. Section 6.5.4 was also updated to specify for Cohort 2 Step 3 participants to resume (non-study provided) cART within 4 weeks following permanent discontinuation of oral study products, and for Cohort 2 Step 4 participants to resume (non-study provided) cART at 8 weeks (±7 days) following permanent discontinuation of injectable study products. These changes were also incorporated into Section 6.7. Section 6.5.4 was also updated that, for Early Termination visits, whole blood (rather than plasma) is to be collected for resistance testing.

43. Section 6.7 was updated to incorporate the timing of Cohort 2 Step 3 and Cohort 2 Step 4 participants resuming (non-study provided) cART following permanent discontinuation of study products, as described above.

44. Section 6.8 was updated with expanded times for eCRF data completion for any Grade 3 or higher adverse event at the study exit visit and for study staff to complete a final study contact.

45. Section 6.12 was updated for consistency with visit schedule and study procedural changes described above.

46. Section 6.15 was clarified that a limited battery of acceptability and tolerability assessments will be conducted for non-English speaking and non-Spanish speaking participants.

47. Section 6.16.2 was updated to clarify that specified tests must be performed at laboratories that are VQA-certified for non-US sites, HIV genotypic and phenotypic resistance sample shipping language was been revised for clarify and to include the Entry visit sample, and to update the PK sample shipping timepoints.

48. Section 7.1.1 has been updated that site investigators must inform the CMC of Grade 3 or higher alanine aminotransferase (ALT).

49. Section 7.1.2 has been updated to include Laboratory Center Representatives, at least one Statistician representative from ViiV, and a medical designee, and at least one Pharmacologist representative from each ViiV and Janssen to the study Clinical Management Committee (CMC).

50. Section 8.1.5 has been updated with clarifications for direct bilirubin testing upon an abnormal total bilirubin test result, as well as to reinforce the requirement of a direct bilirubin test result to assess total hyperbilirubinemia as atazanavir-related.

51. Section 8.2 has been updated with clarification for protocol requirement implementation. For any other abnormality or irregularity reported by the automated read during follow-up that is considered clinically significant by the qualified site clinician, a cardiologist should be consulted, and the CMC notified.

52. Section 8.4 has been updated to clarify that HIV-1 RNA assays must be performed at laboratories that are VQA-certified for non-US sites and clarity.

53. Section 8.7 has been updated for clarity and internal section referencing.
54. Section 9.1 was updated for the revised Cohort 1C target sample size, to clarify the sample size calculations for Cohort 2, and redundant text removed for improved readability. Additionally, in this section, and the evaluable participant definition for analysis purposes has been clarified to:

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

- death that is attributable to the study product/s, OR
- study product-related Grade 3+ events (excluding injection-site AEs) OR
- permanently discontinued from treatment due to study product-related toxicities (regardless of grade) during these weeks of treatment. Note that dose-evaluable participants for dose-finding purposes will be defined separately in Section 9.5.1.3.

55. Section 9.2 has been modified to include the documentation of the CMC assessment of study product related adverse events, the secondary endpoints and outcome measures have been updated to reflect the newly added Secondary Objective described above, and the secondary endpoint for virologic activity has been updated to include HIV-1 RNA >=50 copies/mL.

56. Section 9.4 was revised for Cohort 1C target sample size, with Table 9 updated as shown below.

<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>
<td>0.00, 0.22</td>
</tr>
<tr>
<td>20</td>
<td>0 (0%)</td>
<td>0.00, 0.17</td>
</tr>
<tr>
<td>30</td>
<td>0 (0%)</td>
<td>0.00, 0.12</td>
</tr>
<tr>
<td>35</td>
<td>0 (0%)</td>
<td>0.00, 0.10</td>
</tr>
<tr>
<td>70</td>
<td>0 (0%)</td>
<td>0.00, 0.05</td>
</tr>
<tr>
<td>100</td>
<td>0 (0%)</td>
<td>0.00, 0.04</td>
</tr>
<tr>
<td>15</td>
<td>3 (20%)</td>
<td>0.04, 0.48</td>
</tr>
<tr>
<td>20</td>
<td>4 (20%)</td>
<td>0.06, 0.44</td>
</tr>
<tr>
<td>30</td>
<td>6 (20%)</td>
<td>0.08, 0.39</td>
</tr>
<tr>
<td>35</td>
<td>7 (20%)</td>
<td>0.08, 0.37</td>
</tr>
<tr>
<td>70</td>
<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.
Section 9.5.1.2 has been modified to include the documentation of the CMC assessment of study product related adverse events.

In Section 9.5.1.3, dose finding was clarified to include the term confirmation and dose-evaluable has been specified throughout the section. Additionally, reference to a PK committee was replaced with any relevant protocol team members as being included in dose-finding discussions. This section was also modified to include the definition of dose-evaluable participant (separately from evaluable for analysis purposes), as shown below:

For the purpose of dose-finding, dose-evaluable participants will be defined as participants having been treated exclusively on the dose being evaluated for a given cohort, and having either completed all treatment regimen and completed Week 16 visit or having experienced any of the following:

- death that is attributable to the study product/s, OR
- study product-related Grade 3+ events (excluding injection-site AEs) OR
- permanently discontinued from treatment due to study product-related toxicities (regardless of grade) during the dose-finding period.

Section 9.5.1.3 was also updated with the dose-evaluable term added throughout the dose finding/confirmation algorithm, and the algorithm was revised to clarify the Cohort 1 final analysis, for consistency with other modification described above and for improved readability. The last bullet of the dose finding/confirmation algorithm for Cohort 1 was revised to:

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

Section 9.5.1.3 (Cohort 2) was also updated to reflect the timing of opening Cohort 2 to accrual per interim analysis #2, and to remove redundant text.

Section 9.5.1.3 has also been updated as follows:

a. In sub-section Safety Guidelines for the First 7 Dose-evaluable Participants Started at a Given Dose Level in Each Group in Cohort 1, the second sentence in the first paragraph is removed and the first sentence in the second paragraph is simplified to improve accuracy and eliminate redundancy; and the tenth, 12th and 13th paragraphs are removed because they are not applicable based on the preliminary study data described above.

b. In sub-section Safety Guidelines for the Total Group of Approximately 15-20 (Cohort 1-C) or Approximately 15 (Cohort 1-R) Potentially Dose-evaluable/Dose-evaluable Participants Started at a Given Dose Level in Cohort 1, the first paragraph has been updated to incorporate interim analysis #2, to clarify the criteria required for the starting dose to pass safety guidelines. Additionally, Table 11 was clarified to remove the Cohort 1C and Cohort 1R references.

c. Sub-section 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 has been removed because they are no longer applicable based on the preliminary study data described above.
62. Section 9.5.2 has also been updated to reflect the interim analyses #1 and #2, and to distinguish these from the final Cohort 1 analysis, and the Dose Determination for Cohort 2 sub-section has been removed as it is redundant of Section 9.5.1.3.

63. Section 9.6.2 has been clarified for consistency across protocol sections and improved readability regarding the focus of the primary safety analyses and the timing of performing these analyses. This section is also updated to specify that the safety data will be presented separately for the Q4W vs the Q8W injectable dosing regimens.

64. Section 9.6.3 has been updated to include a newly added secondary analysis for the maintenance of viral suppression, reflective of the Secondary Objectives modification described above, and subsequent sections have been renumbered. This section has also been updated for consistency across protocol sections, clarified that the virologic outcome will be calculated according to the FDA’s Snapshot algorithm and the proportions of participants meeting the criteria for confirmed virologic failure through Week 24 and Week 48 will also be presented, and Table 12 has been modified to:

<table>
<thead>
<tr>
<th>N</th>
<th>% Undetectable RNA</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<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>20</td>
<td>80%</td>
<td>0.56, 0.94</td>
</tr>
<tr>
<td>35</td>
<td>80%</td>
<td>0.63, 0.92</td>
</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>
<tr>
<td>15</td>
<td>90%</td>
<td>0.68, 1.00</td>
</tr>
<tr>
<td>20</td>
<td>90%</td>
<td>0.68, 0.99</td>
</tr>
<tr>
<td>35</td>
<td>90%</td>
<td>0.77, 0.98</td>
</tr>
<tr>
<td>70</td>
<td>90%</td>
<td>0.80, 0.96</td>
</tr>
<tr>
<td>100</td>
<td>90%</td>
<td>0.82, 0.95</td>
</tr>
</tbody>
</table>

65. Section 9.6.4 has been updated to clarify the acceptability and tolerability analyses and remove redundancies. This section has also been modified for clarity and consistency across protocol sections regarding the genotype and phenotype resistance analyses, and a sub-section of Additional
Considerations has been newly added describing that special statistical and data analysis considerations may be warranted due to COVID-19 impact on study data, and further analyses may be conducted as necessary to support regulatory submissions and publications, with such analyses described in an analysis plan.

66. Section 10 has been updated throughout to reflect the Q8W dosing regimen, the revised visit schedule, and the revised PK sampling timepoints, as described above.

67. Section 10.1.1 has also been updated with reference to the Q4W regimen under Version 2.0 and references to the adult studies (ATLAS, ATLAS-2M, and FLAIR), as described above, have been included.

68. Section 10.1.1 has also been clarified that the PK samples collected throughout Cohort 1 will be used to determine PK parameters for CAB or RPV, as applicable, using appropriate analyses, that the PK results from Cohort 1C and Cohort 1R will be used to confirm the use of the adult doses for products in adolescents, and that the exposures observed in the study will be characterized and compared to exposures observed in adult pivotal efficacy trials to aid dosing recommendation in the HIV-1 infected adolescent population.

69. Section 10.1.1, Primary and Other Objectives, has also been clarified for presentation in this subsection as specific to the pharmacology objectives for Cohort 1.

70. Section 10.1.2 has been clarified for improved readability and updated that the overall PK goal for Cohort 2 is to characterize the plasma concentrations, following more prolonged LA dosing in Cohort 2, for confirming their ability to achieve concentrations comparable to those observed in adults.

71. Section 10.1.2, Secondary and Other Objectives, has been clarified for presentation in this subsection as specific to the pharmacology objectives for Cohort 2.

72. Section 10.2 has also been updated with clarified demographic data and available laboratory data to be used in the PK analyses.

73. Section 10.2, Reporting of Assay Data has been updated to clarify the ongoing analyses and planned interim analyses of the Cohort 1 PK data, and the planned timepoints of analyses for the Cohort 2 PK data.

74. Section 10.3 has been updated with the revised concentration targets, reflective of the Q8W dosing regimen and data from the adult studies, as follows:

<table>
<thead>
<tr>
<th>10.3.1.1 Primary Endpoints and Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic output measures as data permit</strong></td>
</tr>
<tr>
<td>• <strong>Cohort 1C – Step 1 PO dosing</strong>: Wk 2 AUC, CL/F, ( C_{max} ), ( T_{max} ), and pre-dose concentrations ((C_0)).</td>
</tr>
<tr>
<td>• <strong>Cohort 1C – Step 2 LA dosing</strong>: Wk 16 concentrations ((C_{16WK})), ( C_{max} ), ( T_{max} ) (Dose 1) and ( C_0 ) prior to IM doses.</td>
</tr>
<tr>
<td>• <strong>Cohort 1R – Step 2 LA dosing</strong>: Wk 16 concentrations ((C_{16WK})), ( C_{max} ), ( T_{max} ) (Dose 1) and ( C_0 ) prior to IM doses.</td>
</tr>
</tbody>
</table>
### 10.3.2 Secondary Endpoints and Outcome Measures

#### 10.3.2.1 Pharmacokinetic outcome measures as data permit

- **Cohort 2**: CAB and RPV pre-dose concentrations following PO administration at Step 3 Wk 2.
- **Cohort 2**: CAB and RPV concentrations following IM administration at Step 4 from Wk 8 (after the first LA injections) to Wk 24 and accumulation ratio (Wk 24 Pre-dose Conc: Wk 8 Pre-dose concentration).
- **Cohort 2**: CAB and RPV concentrations following IM administration at Step 4 from Wk 8 (after the first LA injections) to Wk 48 and accumulation ratio (Wk 48 Pre-dose Conc: Wk 8 Pre-dose concentration).
- **Cohort 2**: CAB and RPV concentrations following IM administration at Step 4 from Wk 16 (after the first LA injections) to Wk 24 and accumulation ratio (Wk 24 Pre-dose Conc: Wk 16 Pre-dose concentration).
- **Cohort 2**: CAB and RPV concentrations following IM administration at Step 4 from Wk 16 (after the first LA injections) to Wk 48 and accumulation ratio (Wk 48 Pre-dose Conc: Wk 16 Pre-dose concentration).

#### 10.3.3 Other Endpoints and Outcome Measures

##### 10.3.3.1 CAB and RPV Pharmacokinetic outcome measures as data permit

- **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).
- **Cohort 1**: CAB or RPV concentrations 8 to 48 weeks following final IM dose.
- **Cohort 2**: CAB and RPV concentrations 8 to 48 weeks following final IM dose.

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75. Section 10.4 has been clarified for consistency across protocol sections and modified to reflect PK model updates for each CAB and RPV, and to clarify the calculated PK parameters to be used in the interim analyses.

76. Section 10.5 has been modified to clarify the PK parameters and the acceptance criteria for each oral CAB, CAB LA, RPV LA.

77. Section 12.2 has been updated to include Janssen representatives among those who may access study records.

78. Section 14.5 has been revised with updated information regarding the Botswana birth outcome surveillance study and findings related to dolutegravir, from the updated Investigator’s Brochure for CAB.

79. Appendix VI *Injectable Study Product Preparation* was newly added to incorporate injectable study product preparation requirements into the protocol.

80. Appendix VII *Guidance for Study Implementation at Sites Experiencing Operational Disruptions Due to COVID-19* was newly added to incorporate implementation guidance to safeguard the health and well-being of study participants and study staff in the context of circulating SARS-CoV-2 and the associated coronavirus disease 2019 (COVID-19).
Modifications to the Sample Informed Consent and Sample Informed Assent Forms

Informed Consent Forms

81. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Introduction, has been modified to include concise and focused presentation of key information to the beginning of each form, in compliance with the Common Rule. This modification has also been incorporated into Appendix II-B (as relevant for Cohort 2), Appendix III-A, and Appendix III-B (as relevant for Cohort 2).

82. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, About the study, has been updated with clarified language regarding HIV as the virus which can lead to AIDS, added listing of countries for study implementation (Botswana, South Africa, Thailand, and Uganda), and Janssen Pharmaceuticals was added to clarify the pharmaceutical support. This modification has also been incorporated into Appendices II-B, III-A, and III-B.

83. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Sections #1, 4, 5, 8, 9, 11, 15, 16, have been updated to reflect changes to the Q8W dosing regimen, the study visit schedule, and changes to study visit procedures relevant to Cohort 1, as described above. Other administrative updates and corrections have been incorporated throughout the form for accuracy, consistency, and clarity. These modifications have also been incorporated into Appendix III-A.

84. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #1, has also been updated to include the countries where RPV oral dosing is approved for adults and adolescents, include the definition of the FDA, and to clarify an objective of the study is to determine if the ARVs are safe and well-tolerated in adolescents. This section was also modified to provide information relating to the information about the FDA action regarding the injectable study products, as follows; this modification has also been incorporated into Appendices II-B, III-A, and III-B:

*RPV shots (600mg and 900mg), CAB pills (30mg), and CAB shots (400mg and 600mg) are now being tested in adults with HIV. The FDA is asking for more information on how these medicines are made before they can approve them in adults. The FDA has no safety concerns regarding these medicines. RPV shots, CAB pills and CAB shots have been approved in Canada for monthly dosing.*

*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.*

85. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #1, has also been clarified that some adolescents have already enrolled and completed Cohort 1 under the Q4W dosing regimen, and that participants enrolling to Cohort 1 will have the Q8W dosing regimen with the associated injection volumes. This modification has also been incorporated into Appendix III-A.

86. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #6 has been updated for consistency across the form that female participants who become pregnant during the study must continue taking their usual ARVs. This modification has also been incorporated into Appendix III-A.
87. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1 has been updated for previously Section #8 to be located as Section #4, for improved readability and flow of information presented; subsequent sections have been renumbered and internal references updated. These modifications and relocating of information have also been incorporated into Appendices II-B, III-A, and III-B.

88. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Sections #9-11 have been clarified for improved readability and as occurring during the correct Cohort 1-Phase number, as follows; these modifications have also been incorporated into Appendix III-A:
   a. Section #9 describing the Cohort 1 Weeks 2 and 4a visits is clarified as occurring during Cohort 1-Phase 1
   b. Section #10 describing the Cohort 1 Week 4b visit is clarified as occurring during Cohort 1-Phase 2
   c. Section #11 describing the Cohort 1 Weeks 5-16 visits is clarified as occurring during Cohort 1-Phase 1

89. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #9 has also been modified to include a description for the potential of an off-site in-person visit and for the potential of a remote visit (by telephone) in the event of site disruptions due to COVID-19. This modification has also been incorporated into Appendices II-B, III-A, and III-B.

90. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #10 has also been modified to include the potential for sites to combine the Week 4a and Week 4b visits, consistent with protocol Section 6.3.3 (for Cohort 1) and 6.4.3 (for Cohort 2). This modification has also been incorporated into Appendices II-B, III-A, and III-B.

91. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #12 has been clarified that the in-depth phone interview is only applicable to U.S. sites, and has been updated for improved readability. These modifications have also been incorporated into Appendices II-B, III-A, and III-B.

92. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #12 has also been updated that the parent/legal guardian may also be asked to complete an in-depth phone interview, and this modification has also been incorporated into Appendix II-B.

93. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #13 has been clarified for improved readability and this modification has also been incorporated into Appendix III-A.

94. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #16 has been clarified for improved readability and to clarify reasons for participants entering long-term safety and washout PK follow-up (LSFU). This section has also been corrected with the timing of pregnant participants being followed per the LSFU visit schedule. These modifications have also been incorporated into Appendix III-A (also Section #16), and Appendices II-B and III-B (Section #15).

95. In Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #17, the section title has been clarified to expand the testing described in the section, the section text has been updated to remove the potential of PK testing being conducted in Ireland, and
resistance testing being conducted in the United States has been added. This section has also been updated to include participants (in addition to their parents) will be given the results of resistance testing and referrals if needed. These modifications have also been incorporated into Appendix III-A (also Section #17), and Appendices II-B and III-B (Section #16).

96. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #18 has been updated to include pregnancy or inability to comply with the birth control requirements, and the participant wishing to discontinue as potential reasons for premature permanent discontinuation of study product, consistent with protocol Section 8.7. Section #18 has also been updated for consistency across the form and per LSFU visit schedule changes. These modifications have also been incorporated into Appendix III-A (also Section #18), and Appendices II-B and III-B (Section #17).

97. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #19 has been updated to include a reference describing the Early Termination visit, consistent with protocol Section 6.5.4. This modification has also been incorporated into Appendix III-A (also Section #19), and Appendices II-B and III-B (Section #18).

98. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Sections #21-24 have been updated to replace the acronym “LA” with “shots” for consistency across the forms, redundant text removed, and other clarifications made for improved readability. These modifications have also been incorporated into Appendices II-B, III-A, and III-B.

99. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #21 has also been updated with added language regarding potential risks from receiving the injection, consistent with updates to the Investigator Brochures for the study product, as shown below. These modifications have also been incorporated into Appendices II-B, III-A, and III-B.

The risks of this are not well understood, but could make CAB or RPV 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 heartbeat, which in severe cases can be life-threatening. In rare cases, symptoms such as feeling lightheaded, numbness or tingling, difficulty breathing, chest or stomach discomfort, sweating, nausea and/or feeling anxious have occurred after an injection with RPV LA. In these cases, high blood levels of RPV have been observed, which may be due to an accidental injection of part of the medication into a blood vessel instead of the muscle. Not all patients in whom an accidental injection in a blood vessel was suspected reported such symptoms. Most of the symptoms resolved within minutes. [Your/your child’s] doctor may need to administer treatment to help resolve these symptoms. 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] 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.

Receiving injections can cause some people to feel lightheaded or feel like they might pass out. Fainting can also occur. This reaction, called a ‘vasovagal reaction’, has been reported with other injectable medicines, and resolves quickly.
100. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #22 has been updated to clarify that the risk information of CAB and RPV is based on their use in adults. These modifications have also been incorporated into Appendices II-B, III-A, and III-B.

101. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #23 has also been modified with a revised Common Side Effects of CAB table, consistent with updates to the Investigator Brochures for the study product, as shown below. These modifications have also been incorporated into Appendices II-B, III-A, and III-B.

### 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>• Headache</td>
<td>• Rash</td>
</tr>
<tr>
<td>• Fever</td>
<td>• Itching</td>
</tr>
<tr>
<td>• Injection Site Reactions</td>
<td>• Vomiting (being sick)</td>
</tr>
<tr>
<td></td>
<td>• Nausea (feeling sick)</td>
</tr>
<tr>
<td></td>
<td>• Stomach pain and discomfort</td>
</tr>
<tr>
<td></td>
<td>• Problems sleeping</td>
</tr>
<tr>
<td></td>
<td>• Abnormal dreams/nightmares</td>
</tr>
<tr>
<td></td>
<td>• Anxiety</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>• Diarrhea</td>
</tr>
<tr>
<td></td>
<td>• Muscle pain</td>
</tr>
<tr>
<td></td>
<td>• Lack of energy</td>
</tr>
<tr>
<td></td>
<td>• Increase in the level of enzymes made in the muscles (creatine phosphokinase)</td>
</tr>
<tr>
<td></td>
<td>• Weight increased</td>
</tr>
</tbody>
</table>

102. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #24 has also been modified with a revised Common Side Effects of RPV and Uncommon Side Effects of RPV table, consistent with updates to the Investigator Brochures for the study product, as shown below. This modification has also been incorporated into Appendix III-A.

### Common Side Effects of RPV

<table>
<thead>
<tr>
<th>Common Side Effects of RPV</th>
<th>Uncommon Side Effects of RPV</th>
</tr>
</thead>
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<td>• Headache</td>
<td>• Depressed mood</td>
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<td>• Feeling light headed (dizziness)</td>
<td>• Stomach discomfort</td>
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<tr>
<td>• Rash</td>
<td>• Immune reconstitution syndrome (this can be an overreaction of the body’s recovering defense system to a previously present infection, or problems in the immune system)</td>
</tr>
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<td>• Nausea (feeling sick to the stomach)</td>
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<td>• Fatigue (tiredness, lack of energy)</td>
<td></td>
</tr>
<tr>
<td>• Dry mouth</td>
<td></td>
</tr>
</tbody>
</table>
103. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #24, Abnormal blood test has been updated to align with the DAIDS RPV risk language.

104. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #25, Possible effects on pregnancy or unborn babies, first paragraph, has been modified with updated RPV risk during pregnancy, consistent with updates to the Investigator Brochures for the study product, as shown below. This modification has also been incorporated into Appendices II-B, III-A, and III-B.

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 is safe in pregnancy. RPV does not appear to be a risk to pregnancy and the developing baby based on the information we know now, but additional data are still being collected.

105. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #25, Immune reconstitution syndrome, was updated to include an example of a disease which could be indicative of immune reconstitution syndrome. Additionally, Mental Illness has been updated to include “or Depression” in the sub-heading title, with the text updated to align with DAIDS RPV risk language. These modifications have also been incorporated into Appendices II-B, III-A, and III-B.

106. Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #26 was modified with added language regarding information collected from this study may be used for other research in the future including anonymized information about the consenting participant. This modification has also been incorporated into Appendices II-B, III-A, and III-B.

107. In Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #27, the potential benefit of the study drugs possibly lowering the participant’s viral load was removed. This modification has also been incorporated into Appendices II-B, III-A, and III-B.

108. In Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #27, the potential benefits of gaining a better understanding of the participant’s health and HIV care, and the possible benefit of early access to the Cohort 2, if the participant qualifies were added. This modification has also been incorporated into Appendix III-A.

109. In Appendix II-A, Sample Parental Informed Consent Form for Participation in Cohort 1, Section #29, Janssen Pharmaceuticals has been added as an entity that may review study records. This modification has also been incorporated into Appendices II-B, III-A, III-B (Section 29), and Appendices IV-A, IV-B, V-B, V-C (Other information about the study).

110. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, About the Study has been clarified that access to the study products after the Week 96 visit will be external to the study. This clarification has also been incorporated into Appendix III-B.

111. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, Sections #1, 4, 5, 8, 9, 10, 11, 12, 14, and 15, have been updated to reflect changes to the Q8W dosing regimen, the study visit schedule, and changes to study visit procedures relevant to Cohort 2, as described
above. Other administrative updates and corrections have been incorporated throughout the form for accuracy, consistency, and clarity. These modifications have also been incorporated into Appendix III-B.

112. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, Section #1 has also been clarified that participants enrolling to Cohort 2 will have the Q8W dosing regimen with the associated injection volumes. This modification has also been incorporated into Appendix III-B.

113. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, Sections #9-11 have been clarified for improved readability and as occurring during the correct Cohort 2-Phase number, as follows; these modifications have also been incorporated into Appendix III-B:
   a. Section #9 describing the Cohort 2 Weeks 2 and 4a visits is clarified as occurring during Cohort 2-Phase 1
   b. Section #10 describing the Cohort 2 Week 4b visit is clarified as occurring during Cohort 2-Phase 2
   c. Section #11 describing the Cohort 2 Weeks 5-96 visits is clarified as occurring during Cohort 2-Phase 2.

114. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, Section #11 has also been updated to include a description for the potential of short-term oral bridging as well as the potential for interim injection visit(s) upon resuming injectable study product. This modification has also been incorporated into Appendix III-B.

115. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, Section #15 has been updated to remove an incorrect reference to the Cohort 1 Step 2 Week 16 visit.

116. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, Section #19 has been updated with clarifications to pharmaceutical support. This modification has also been incorporated into Appendix III-B.

117. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, *Risks of the study*, first three paragraphs have been updated with clarifications to correct the risk of switching ARVs to correspond to Cohort 2-Phase 1 (when participants stop their pre-study cART regimen), and Cohort 2-Phase 3 (when participants will resume a non-study provided cART regimen).

118. Appendix II-B, Sample Parental Informed Consent Form for Participation in Cohort 2, Section #24 has also been modified with a revised Common Side Effects of RPV and Uncommon Side Effects of RPV table, consistent with updates to the Investigator Brochures for the study product, as shown below. This modification has also been incorporated into Appendix III-B.

<table>
<thead>
<tr>
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<td>Vomiting</td>
<td>infection, or problems in the immune</td>
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<tr>
<td>Abdominal (belly) pain</td>
<td></td>
</tr>
</tbody>
</table>
- Increase in the level of liver enzymes
- Decreased appetite
- Depression
- Abnormal dreams
- Fatigue (tiredness, lack of energy)
- Dry mouth
- Anxiety
- Stomach pain

- Hepatotoxicity
- Weight increased

119. Appendix II-C, Sample Parental Informed Consent Form for Specimen Storage and Future Use, Section #3 has been modified with added language that whole genome sequencing will not be performed in the study. This modification has also been incorporated into Appendix III-C.

120. Appendix II-C, Sample Parental Informed Consent Form for Specimen Storage and Future Use, Section #4 has been clarified with added language that any linkage between a participant’s study data and personal identifiers will not be shared external to the site. This modification has also been incorporated into Appendix III-C.

Informed Assent Forms

121. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, Introduction and What happens in the study have been updated for improved readability. These modifications have also been incorporated into Appendix IV-B.

122. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, About the study has been updated that oral cabotegravir, injectable cabotegravir long-acting and injectable rilpivirine long-acting are investigational and are not yet approved by the FDA for the treatment of HIV infection, and to include the definition of the FDA. These modifications have also been incorporated into Appendix IV-B.

123. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, About the Study, First phase of the study, Second phase of the study, and Long-term safety follow-up phase of the study have been updated to reflect the Q8W dosing regimen, study visit schedule changes, and study visit procedural changes relevant to Cohort 1, as described above, as well as specifying that the qualitative phone interviews are only applicable to U.S. sites. First phase of the study has also been updated to specify that RPV pills should be taken with a meal. These modifications and have also been incorporated into Appendix IV-B, as relevant to Cohort 2.

124. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, Second phase of the study has also been modified to include the potential for sites to combine the Week 4a and Week 4b visits, consistent with protocol Section 6.3.3 (for Cohort 1) and 6.4.3 (for Cohort 2). This modification has also been incorporated into Appendix IV-B.

125. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, Risks of the study has been modified to include the location of administering the injections, and the risks associated with high levels of RPV LA. This modification has also been incorporated into Appendix IV-B.

126. Appendix IV-A, Sample Informed Assent Form for Participation in Cohort 1, Second phase of the study has also been modified to include a description for the potential of an off-site in-person visit
and for the potential of a remote visit (by telephone) in the event of site disruptions due to COVID-19. This modification has also been incorporated into Appendix IV-B.

127. Appendix IV-B, Sample Informed Assent Form for Participation in Cohort 2, *Second phase of the study* has been updated to include a description for the potential of short-term oral bridging as well as the potential for interim injection visit(s) upon resuming injectable study product.

128. Appendix IV-C, Sample Informed Assent Form for Specimen Storage and Future Use for Participants, *What happens with extra samples* has been modified with added language that whole genome sequencing will not be performed in the study.

129. Appendix IV-C, Sample Informed Assent Form for Specimen Storage and Future Use for Participants, *Risks and benefits* has been clarified with added language that any linkage between a participant’s study data and personal identifiers will not be shared external to the site.

130. Appendix V-B, Parent/Caregiver Phone Interview Sample Informed Consent Form, *Your role in the study* has been updated to reflect changes to the study visit schedule relevant to Cohort 1, as described above. These modifications have also been incorporated into Appendix V-C.