TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase III, randomized, multicenter, parallel-group, non-inferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current INI- NNRTI-, or PI-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed

Compound Number: GSK1265744

Development Phase: III

Effective Date: 02-NOV-2017

Protocol Amendment Number: 04

Author (s):

PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N252007_00	2016-MAY-26	Original
2015N252007_01	2016-SEP-16	Amendment No. 1
The purpose of this amendment is to support country-specific requirements for South Korea including an update to inclusion criteria age for local regulatory requirements and the addition of study investigational product labels within Appendix 8.		
2015N252007_02	2016-NOV-02	Amendment No. 2
The purpose of this amendment is to support country-specific requirements for Sweden based on local regulatory requirements and to provide additional protocol details and clarifications requested by the MPA.		
2015N252007_03	2016-DEC-13	Amendment No. 3
The reasons for this amendment were to: update medical monitor/SAE contact information; provide additional clarity for assessments to be conducted during the Extension Phase; add text to instruct contact of the Medical Monitor upon the occurrence of rash during the CAB + RPV oral lead-in period; specify a secondary lipid objective and endpoint within the study objectives; provide clarity around dosing at the Day 1 visit; allow serum pregnancy testing instead of urine testing in the event that urine testing is not available; provide clarification that cabotegravir and rilpivirine exposure may persist for more than one year following IM injections, emphasize that participants should continue to use HAART for at least one year following the last CAB + RPV injection, and that female participants of childbearing potential must continue to use adequate contraception for at least one year after the last CAB + RPV injection; expand the allowance of short treatment courses of topical, inhaled, or intranasal glucocorticoids to 21 days or less; add additional guidance for the definition of a change in ART regimen for inclusion/exclusion criteria; provide additional guidance on when to contact the Medical Monitor upon a serofast RPR result for screening syphilis test; clarify language within exclusion criteria #9; added text regarding the treatment assignment randomization schedule; remove a requirement to record within the eCRF how frequently IP was taken on average and the requirement to record any treatment delays or dose reductions of IP; add text to indicate that drugs known to cause Torsade des Pointes (TdP) should be used with caution with rilpivirine; remove limits on the duration for use of topical imiquimod; add clarity around reflexive testing for HBV DNA for participants with positive anti HBc and negative HBsAg and negative anti-HBs results; add temperature collection as part of vital signs to the Time and Events table; add requirement that all sites should have a plan in place for managing possible risks for suicide related events; clarify text regarding PK sample window collection; clarify text for patient reported outcome endpoints and timings for completion of questionnaires relative to other clinical assessments and procedures, add clarification for prohibited medication information; remove information in the Appendix		

requiring collection of pregnancy information for female partners of male study participants; incorporate updates from country-specific amendments No 1, and No 2. into a global protocol amendment; add text that additional details of the injection device used by sites for IM administration including, but not limited to functional performance, may also be collected within the eCRF; clarify that commercially availability of CAB LA + RPV LA includes availability through local public/government health sectors; add allowance that in exceptional circumstances, local labs can be reviewed and approved by the Medical Monitor for consideration of participant eligibility; add information that Screening HLA-B*5701 result is not required to inform eligibility status; add other minor corrections and edits to protocol text.		
2015N252007_04	2017-NOV-02	Amendment No. 4
The reason for amendment 4 is to acknowledge the potential rollover of eligible 201585 (ATLAS) study participants following the Week 52 visit and completion of the primary endpoint to the 207966 (ATLAS-2M) study examining the efficacy, safety and tolerability of CAB LA + RPV LA administered every 4 weeks (Q4W) compared to CAB LA + RPV LA administered every 8 weeks (Q8W). Specifications for the procedural rollover of 201585 participants are included within amendment #4. Due to the planned transition of eligible participants to ATLAS-2M following the Week 48 primary endpoint, the snapshot virologic response at Week 96 and in the Extension Phase for ATLAS is no longer valid and has been replaced with the proportion of participants with plasma HIV-1 RNA < 50 c/mL over time including Week 96. Exploratory analyses evaluation the effect of patient characteristics on virologic and immunologic responses in the treatment arms are also limited to a Week 48 analysis. The reporting timeline of pregnancy event and follow-up pregnancy form has been updated from 2 weeks to 24 hrs of identification of a pregnancy event, and within 24 hrs of investigator awareness of pregnancy outcome, respectively. Updated references for the cabotegravir and rilpivirine investigator brochures have been added.		

SPONSOR SIGNATORY

PPD

Date 4/2/17

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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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This study is sponsored by ViiV Healthcare. GlaxoSmithKline is implementing and managing all aspects of this study on behalf of ViiV Healthcare.

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s):

IND No. 109,678;

EudraCT No. **2016-001647-39**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201585

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201585

Rationale

The 201585 (Antiretroviral Therapy as Long Acting Suppression-ATLAS study) is being conducted to establish if human immunodeficiency virus type 1 (HIV-1) infected adult participants with current viral suppression on a regimen with 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent, remain suppressed upon switching to a two-drug intramuscular (IM) long-acting (LA) regimen of cabotegravir (CAB) and rilpivirine (RPV). This study is designed to demonstrate the non-inferior antiviral activity of switching to CAB LA 400 mg + RPV LA 600 mg every 4 weeks (monthly) for 48 weeks (4 weeks oral CAB + RPV, 44 weeks LA therapy) compared to continuation of current antiretroviral therapy (current ART). 201585 (ATLAS) will also provide important long-term antiviral activity, safety, tolerability and patient satisfaction through Week 96. Additionally, participants initially randomized to continue current ART will be given an option to switch to LA therapy at Week 52. Eligible participants (HIV-1 RNA <50 c/mL at Week 48) will transition to LA dosing, beginning with 4 weeks oral CAB + RPV therapy at Week 52, and receive the first IM CAB LA + RPV LA injections at Week 56.

201585 (ATLAS) is being conducted in parallel with the 201584 (the First Long-Acting Injectable Regimen- FLAIR study) with the aim to pool data generated from the current study with study 201584, in order to evaluate key program objectives.

Objectives/Endpoints

Objectives	**Endpoints**
Primary	
To demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of current first line antiretroviral regimen over 48 weeks in HIV-1 infected antiretroviral therapy (ART)-experienced participants	• Proportion of participants with a 'virologic failure' endpoint as per Food and Drug Administration (FDA) Snapshot algorithm at Week 48 (Intent-to-Treat Exposed [ITT-E] population).
Secondary	
To demonstrate the antiviral and immunologic activity of switching to intramuscular CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of current ART	• Proportion of participants with Plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] population). • Proportion of participants with plasma HIV-1 RNA <200 c/mL at Week 48 using the

Objectives	**Endpoints**
	Snapshot algorithm (ITT-E population) • Proportion of participants with confirmed virologic failure (two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) at Week 48 • Absolute values and change from Baseline in plasma HIV-1 RNA (log_{10} c/mL) at Week 48. • Absolute values and change from Baseline in CD4+ lymphocyte count at Week 48 • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death over 48 Weeks
To evaluate the safety and tolerability of switching to CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of current ART	• Incidence and severity of adverse events (AEs) and laboratory abnormalities over time including Week 48 • Proportion of participants who discontinue treatment due to AEs over time including Week 48 • Absolute values and changes in laboratory parameters over time including Week 48
To evaluate the effects of CAB LA + RPV LA every 4 weeks on fasting lipids over time compared to continuation of current ART over time.	• Change from Baseline in fasting lipids over time including Week 48 and Week 96.
To assess viral resistance in participants experiencing protocol-defined virologic failure	• Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV and other on-study ART at Week 48
To assess the impact of Baseline third agent treatment class (INI, NNRTI, or PI) on efficacy, safety, tolerability, and viral resistance of CAB LA + RPV LA compared to continuation of current ART	<u>By Baseline third agent treatment class:</u> • Proportion of participants with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 48 (Intent-to-Treat Exposed [ITT-E] population).

Objectives	**Endpoints**
	• Proportion of participants with Plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm (Intent-to-Treat Exposed [ITT-E] population) • Incidence and severity of select AEs and laboratory abnormalities over time including Week 48 • Proportion of participants who discontinue treatment due to AEs over time including Week 48 • Absolute values and changes in select laboratory parameters over time including Week 48 • Incidence of observed genotypic and phenotypic resistance to current antiretroviral regimen and to CAB or RPV for participants meeting confirmed virologic failure
To characterize CAB and RPV concentrations and population pharmacokinetics and identify important determinants of variability.	• Plasma PK parameters for CAB LA and RPV LA (when evaluable, $C_{trough,}$ concentrations post dose [~Cmax], and area under the curve [AUC]) • Demographic parameters including, but not limited to, age, sex, race, body weight, body mass index, and relevant laboratory parameters will be evaluated as potential predictors of inter- and intra-participant variability for pharmacokinetic parameters
To evaluate the antiviral and immunologic effects, safety, tolerability, and viral resistance of CAB LA + RPV LA for participants during the Extension Phase • For participants randomized to CAB LA+ RPV LA at Day 1 • For participants electing to transition to CAB LA + RPV LA in the Extension	• Proportion of participants with plasma HIV-1 RNA <50 c/mL over time including week 96 (Observed Case). • Proportion of participants with confirmed virologic failure (two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) through Week 96

Objectives	**Endpoints**
Phase	• Absolute values and change from Baseline in plasma HIV-1 RNA over time including Week 96 • Absolute values and changes from Baseline in CD4+ cell counts over time including Week 96 • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death) • Incidence and severity of AEs and laboratory abnormalities over time including Week 96 • Proportion of participants who discontinue treatment due to AEs over time including Week 96 • Absolute values and changes in laboratory parameters over time including Week 96 • Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on study ART at Week 96
To assess the acceptance of pain and injection site reactions following injections	• Change from Week 5 in Dimension scores ("Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of iNjection questionnaire (PIN) • Proportion of participants considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the Perception of iNjection questionnaire (PIN)
To assess degree of health-related quality of life	• Change from Baseline in HR QoL using the

Objectives	Endpoints
(HRQoL)	HIV/AIDS-targeted quality of life questionnaire (HAT QoL) short form at Week 24, Week 48, Week 96 (or Withdrawal).
To assess the health status	• Change from Baseline in health status at Week 24, Week 48, and Week 96 (or Withdrawal) using the 12-item Short Form Survey (SF-12). .
To assess treatment satisfaction of CAB LA + RPV LA compared to continuation of current ART	• Change from baseline in total "treatment satisfaction" score, and individual items scores of the HIVTSQs at Weeks 4b, 24, 44, 96 (or Withdrawal) • Change in treatment satisfaction over time using the HIVTSQc at Week 48 (or Withdrawal)
To assess treatment acceptance	• Change from Baseline in treatment acceptance at Week 8, Week 24, Week 48, Week 96 (or Withdrawal) using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire
To assess tolerability of injections	• Change from Week 4b in tolerability of injection at Week 5, Week 40, Week 41, and Week 96 using the Numeric Rating Scale (NRS) within the CAB + RPV LA arm.

Overall Design

201585 (ATLAS) is a Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of a two drug regimen of CAB LA + RPV LA compared with maintenance of current ART. Approximately 570 adult HIV-1 infected patients who are on a stable ARV regimen containing 2 NRTIs plus an INI, NNRTI, or a PI will be randomized 1:1 to continue current ART or be switched to the CAB LA + RPV LA regimen through 52 weeks. The randomized portion of the study will continue with an Extension Phase up to at least 96 weeks.

Participants will be randomized (1:1) at Day 1 to either continue on current ART or to discontinue current ART and begin oral therapy with CAB 30 mg + RPV 25 mg once daily to determine individual safety and tolerability prior to administration of CAB LA +

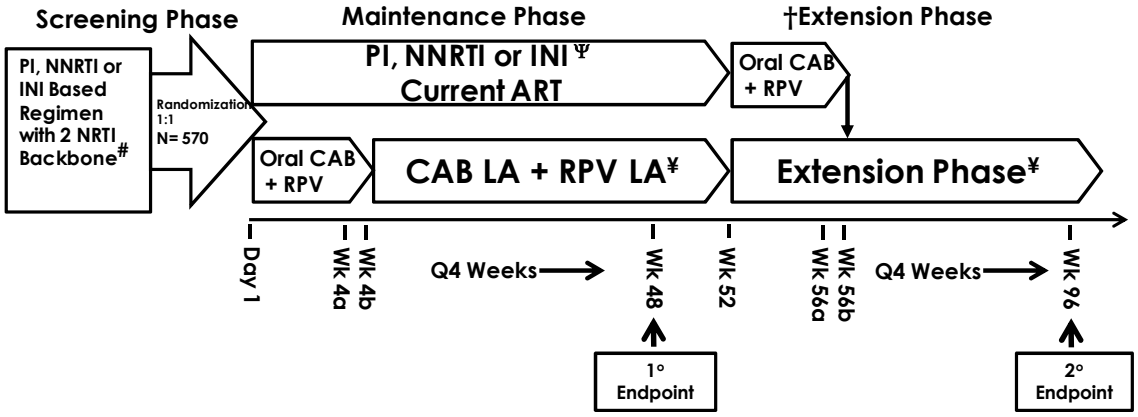
RPV LA. Current ART dosing on Day 1 is recommended to occur after randomization to avoid overlap of regimens (in the event that the participant is assigned to the CAB LA + RPV LA treatment arm). However, if the participant takes current ART prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1.

At the Week 4a visit, safety assessments (including e.g., clinical chemistries) will be performed as per the Time and Events Table. At visit Week 4b, participants will return to the clinic, take the last dose of oral CAB + RPV, and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). The first injection visit with IM CAB LA 600 mg and RPV LA 900 mg (Week 4b) can be performed once central lab results are available and safety parameters are reviewed. The second and third IM injections with CAB LA 400 mg and RPV LA 600 mg will be performed at Week 8 and Week 12. There will be a one week dosing window for the second and third IM injections such that the second injection occurs within the window of Week 7 and Week 8 but no later than Week 8 and the third injection occurs within the window of Week 11 and Week 12 but no later than Week 12. Subsequent injections with CAB LA 400 mg and RPV LA 600 mg will occur every 4 weeks thereafter (±7 days from the visit schedule) allowed but not preferred. In addition, starting after the Week 12 injection, efforts should be made to limit time between injection visits to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds or is projected to exceed 5 weeks.

Randomization will be stratified by baseline third agent class (PI, INI, or NNRTI), and gender at birth The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, ITT-E population) is a key secondary endpoint comparison.

The sample size of 285 per arm is such that the study has approximately 97% power to demonstrate non-inferiority in the proportion of participants with snapshot virologic failure at Week 48 using a 6% margin, assuming a true 3% failure rate for CAB LA + RPV LA and a 2% failure rate for the current ART control arm and using a 2.5% one-sided alpha level. This sample size is primarily chosen so that the pooled analysis of data from this study and study 201584 (combined sample size of 570 per arm) will have 90% power to show non-inferiority for the proportion of participants with Snapshot virologic failure at Week 48 using a 4% non-inferiority margin, under the assumptions described above.

201585 (ATLAS) Study Design Schematic



N=570, randomized 1:1 to each arm and stratified by baseline 3rd Agent class and gender at birth.
# Must be on uninterrupted current regimen (either the initial or second cART regimen) for at least 6 months prior to Screening.Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening. No history of virologic failure. No evidence of viral resistance based on the presence of any resistance-associated major INI, or NNRTI mutation (except K103N) from prior genotype assay results. No current or prior history of etravirine use.
ΨINI based regimen excludes abacavir/dolutegravir/lamivudine (TRIUMEQ), and INI therapy will be capped at approximately 40% of study enrolment for current ART
†Optional Extension Phase to CAB LA + RPV LA at Wk 52 for participants randomized to current ART
¥Participants who withdraw from IM arm must go into 52 week long term follow up phase

Treatment Arms and Duration

Screening Phase (Up to 35 days)

Informed consent must be obtained prior to any study procedures, including any Screening assessment.

Participants will be involved in a screening period of up to 35 days. Participants may be re-screened once. Participants who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be randomized as soon as all eligibility requirements have been confirmed at the site.

Maintenance Phase (Day 1 up to Week 52)

At Day 1, Eligible participants will be randomized 1:1 to:

- Oral CAB 30 mg + RPV 25 mg once daily for four weeks (participants will be assessed for safety and tolerability after four weeks). At Week 4a, participants will have the assessments completed as per the Time and Events Table including clinical chemistries At visit Week 4b, participants will return to the clinic, take the last dose of oral CAB + RPV, and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). The first injection visit with IM CAB LA 600 mg and RPV LA 900 mg (Week 4b) can be performed once central lab results are available and safety parameters

are reviewed. The second and third IM injections with CAB LA 400 mg and RPV LA 600 mg will be performed at Week 8 and Week 12 with a one week dosing window allowed for the second and third IM injections such that the second injection occurs within the window of Week 7 and Week 8 but no later than Week 8 and the third injection occurs within the window of Week 11 and Week 12 but no later than Week 12. Subsequent injections with CAB LA 400 mg and RPV LA 600 mg will occur every 4 weeks thereafter with a two week dosing window (±7 days from the visit schedule) allowed but not preferred. In addition, starting after the Week 12 injection, efforts should be made to limit time between injection visits to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds or is projected to exceed 5 weeks.

OR

- Continue on current ART regimen for at least 52 weeks. Participants who successfully complete Week 52 (without meeting study defined withdrawal criteria and who remain virologically suppressed (HIV-1 RNA <50 c/mL) will be given the option to switch to CAB LA + RPV LA in the Extension Phase, or be withdrawn from the study.

Randomization will be stratified by baseline third agent class (INI, NNRTI, or PI), and gender at birth.

Extension Phase

Participants Entering from the CAB LA + RPV LA Arm

All participants who successfully complete 52 weeks of treatment in the Maintenance Phase will continue to have access to both CAB LA and RPV LA in the Extension Phase until study treatment is either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 4 weeks as per the Time and Events Schedule

Participants Entering from the Current ART Arm

Participants randomized to continue on current ART will have the option to either continue study participation by switching to CAB LA + RPV LA in the Extension Phase, or to complete their study participation at Week 52 (no withdrawal visit needed).

Participants who choose to continue on to the Extension Phase will need to be assessed for eligibility to begin the CAB LA + RPV LA regimen. Participants will continue on their current ART Maintenance regimen while eligibility is being confirmed. All participants with an undetectable HIV-1 RNA (<50 c/mL) result from the Week 48 visit are eligible to enter the Extension Phase. A single repeat of HIV-1 RNA for any participant with a HIV-1 RNA ≥50 c/mL and < 400 c/mL at Week 48 must be performed. The retest should be scheduled as soon as possible (but no later than 4 weeks from the Week 48 visit). Participants with HIV-1 RNA <50 c/mL upon retest are eligible to enter

the Extension Phase. Participants with HIV-1 RNA ≥400 c/mL at Week 48 are not eligible to enter the Extension Phase, will not be allowed a repeat to determine eligibility, and will therefore be withdrawn from the study.

Participants eligible to enter the Extension Phase will begin a 4 week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily at Week 52. At Week 56a, participants will have assessments completed as per the Time and Events Table including clinical chemistries. At visit Week 56b, participants will return to the clinic, take the last dose of oral CAB + RPV, and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). The first injections can be performed as soon as central lab results from the Week 56a visit become available and safety parameters are reviewed. The second and third IM injections with CAB LA 400 mg and RPV LA 600 mg will be performed at Week 60 and Week 64. There will be a one week dosing window for the second and third IM injections such that the second injection occurs within the window of Week 59 and Week 60 but no later than Week 60 and the third injection occurs within the window of Week 63 and Week 64 but no later than Week 64. Subsequent injections with CAB LA 400 mg and RPV LA 600 mg will occur every 4 weeks thereafter (±7 days from the visit schedule allowed but not preferred). Following the Week 64 injection, the interval between injection visits should be limited to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds or is projected to exceed 5 weeks.

Participants will continue study treatment until CAB LA and RPV LA are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 4 weeks as per the Time and Events Schedule.

Participants not eligible to enter the Extension Phase will end their study participation (Week 52 will be the last study visit, no withdrawal visit needed). Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for participants that do not qualify for the Extension Phase.

Long-Term Follow-Up Phase – IM Regimen Only

Any participant who receives at least a single dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. **Investigators must discuss the choice of the follow-up HAART regimen with the Medical Monitor prior to initiating the new regimen with the participant. HAART therapy should be initiated within 4 weeks of the last injection.** The LTFU will begin the day of the last CAB LA and/or RPV LA dose and continue for 52 weeks, or until CAB LA + RPV LA is locally approved and commercially available. These participants will not complete a Withdrawal visit, but will instead move directly into the Long-Term Follow-Up Phase as per the Time and Events Schedule. In addition, for participants who withdraw during the Long-Term Follow-Up Phase, the final visit will be considered the study withdrawal visit.

Participants will be assessed with clinic visits at months 1, 3, 6, 9 and 12 during the Follow-Up Phase. Female participants of child bearing potential must continue to use adequate contraception methods (see Study Procedures Manual for list of accepted forms of contraception) for the entire year of follow up.

In order to assure that participants have access to HAART during the Long-Term Follow-Up Phase, GSK may supply HAART regionally or reimbursement will be provided as needed during this phase. The Long-Term Follow-Up Phase may be shortened at any time during the study for various reasons, e.g., better understanding of risks of development of resistance as CAB and RPV exposures decline, regulatory approval and commercial availability, end of study timings, etc.

This phase is considered study participation and participants will be followed on study during this time. A withdrawal visit is not required for participants who do not complete the Long-Term Follow-Up Phase. The participants' last on study visit will be considered as their withdrawal visit.

Dose Modifications:

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during the study beyond what is allowed within the protocol. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements is essential and required for study conduct.

In exceptional circumstances, and in consultation with the Medical Monitor, Investigators may provide oral CAB and/or RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. Should a participant need "oral bridging", sites must contact the Medical Monitor for guidance on treatment strategies prior to a missed CAB LA + RPV LA dose. Should a participant not notify the site in advance, the Medical Monitor must be contacted for further treatment guidance.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM), which is available on the online Study Web Portal. The SPM will provide the site personnel with administrative and detailed technical information.

207966 (ATLAS-2M) Rollover Option

The 207966 (ATLAS-2M) study is being conducted in approximately 1020 participants to establish if human immunodeficiency virus type 1 (HIV-1) infected adults with current viral suppression (HIV-1 RNA <50 c/mL) remain suppressed upon administration of a two-drug intramuscular (IM) long-acting (LA) regimen of cabotegravir (CAB) and rilpivirine (RPV) administered every 8 weeks (Q8W; every 2 months). The ATLAS-2M study is designed to demonstrate the non-inferior antiviral activity of CAB LA 600 mg + RPV LA 900 mg administered every 8 weeks compared with CAB LA 400 mg + RPV LA 600 mg administered every 4 weeks (Q4W; monthly) over a 48-week treatment period. ATLAS-2M will also provide comparative data on antiviral activity, safety, tolerability, and patient satisfaction through Week 96. It is anticipated that the majority of ATLAS participants will transition to the ATLAS-2M study.

Upon local approval and implementation of the ATLAS-2M trial, investigators will approach all potentially eligible ATLAS participants with the optional consent for ATLAS-2M participation and potential randomization to the CAB LA + RPV LA Q4W or Q8W regimen. If a participant can not or chooses not to transition to the ATLAS-2M trial, or is otherwise determined to be ineligible for ATLAS-2M, the participant can elect to continue participation in ATLAS trial without limitations and according to the approved protocol design.

Eligibility to transition to ATLAS-2M at Week 52 (at the earliest) will be determined once the final central lab results from ATLAS, following (at minimum) completion of the ATLAS Week 48 visit are available and safety parameters have been reviewed. Separate Screening Labs will be utilized to inform eligibility for ATLAS-2M; however, in some occasions and upon consultation with the Medical Monitor, individual lab results and safety data from the final visit of the ATLAS study can be considered towards informing eligibility for the ATLAS-2M study as long as all other screening and eligibility criteria are met. Following randomization to ATLAS-2M, participants will follow all schedules and activities of the ATLAS-2M trial and no withdrawal or additional follow-up activities for the ATLAS study are required.

Study Completion

Participants are considered to have completed the study if they remain on therapy (i.e., have not permanently discontinued IP) and satisfy one of the following:

- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including the Week 52 visit, and did not enter the Extension Phase;

- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including the Week 52 visit, and entered and completed the Extension Phase (defined as remaining on study until commercial supplies of CAB LA + RPV LA become locally available or development of CAB LA + RPV LA is terminated or participant rolls over into ATLAS 2M).

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be instituted to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of subjects and to protect the scientific validity of this study and study 201584.

The IDMC will evaluate accumulating efficacy, tolerability, safety and PK of CAB LA + RPV LA at predetermined times during the study. An interim analysis will be performed for the IDMC to evaluate the efficacy of CAB LA + RPV LA prior to the final analysis. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

The interim futility analysis will be performed with the intent of having approximately 50% of participants reaching Week 24 and providing sufficient lead time to allow the IDMC to review the data prior to any participants reaching the Week 48 visit. A futility rule based on Bayesian posterior predictive probability approach will be applied to assess the probability that CAB LA + RPV LA injectable regimen demonstrate non-inferiority to the continued current ART arm given the partial data set. The sponsor will remain blinded to this analysis.

In addition, the IDMC may also monitor the incidence of participants meeting Confirmed Virologic Failure (CVF) criteria through Week 48 to ensure that participants are not being sub-optimally treated in the CAB LA + RPV LA arm.

Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

Type and Number of Participants

The target population to be enrolled is virologically suppressed participants with HIV-1 infection on stable antiretroviral therapy (ART).

Assuming 30% screen failure rate, approximately 815 HIV-1-infected adult participants will be screened to achieve 570 randomized participants for a total of 285 participants per treatment group. Participants will be enrolled from multiple countries which may include Argentina, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the United States.

Randomization will be stratified by baseline third agent class (PI, INI, or NNRTI) and gender at birth. The 201585 (ATLAS) study will exclude enrolment of participants treated with abacavir/dolutegravir/lamivudine (TRIUMEQ) and will aim to limit enrolment of participants on an INI to approximately 40%. TRIUMEQ comparator data along with the majority of INI comparator data for the CAB LA + RPV LA program will be generated from 201584 (FLAIR) and will be included within a planned pooled analysis with 201585 (ATLAS) results. A goal of this study is to enrol populations who are underrepresented in clinical studies including approximately 25% women. To provide sufficient data to determine whether either gender is correlated with treatment response, sites are expected to take into account gender in their screening strategies.

Analysis

The primary analysis at Week 48 will take place after the last participant has had their Week 48 viral load assessed, including a retest if required. The primary analysis method for the proportion of participants defined as Snapshot virologic failures at Week 48 will be a Cochran-Mantel Haenszel test stratified by randomization stratification factors. A non-inferiority margin of 6% will be used for this comparison, where if the upper limit of the 95% confidence interval (CI) of the difference in failure rate between the two study arms is less than 6%, non-inferiority will be demonstrated.

Assuming the true virologic failure rate is 3% for the CAB LA + RPV LA injectable regimen and 2% for the current ART arm, this would provide approximately 97% to

show non-inferiority at a 2.5% one-sided significance level. If we observe a 2% failure rate for the current ART arm, then non-inferiority would be declared if we observe a 5% or lower failure rate for the CAB LA + RPV LA arm (i.e. an observed treatment difference less than 3 percentage points for [CAB LA + RPV LA] – current ART).

A key secondary analysis will evaluate the proportion of responders (HIV-1 RNA <50 c/mL per Snapshot) at Week 48 using a Cochran-Mantel Haenszel test stratified by randomization stratification factors. A non-inferiority margin of -10% will be used for this secondary comparison, where if the lower limit of the 95% confidence interval (CI) of the difference in responder rate between the two study arms is greater than -10%, non-inferiority will be demonstrated. Assuming true response rates for the CAB LA + RPV LA arm and current ART arm are both 87%, the sample size of 285 per arm will provide at least 94% power to show non-inferiority at a 2.5% one-sided significance level.

In addition, the data from this study, together with data from a separate study, 201584, will be combined to assess non-inferiority using a 4% non-inferiority margin. The combined sample size from both studies (570 pooled per arm) will provide 90% power, under the assumptions described above, to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL) at Week 48.

201585 (ATLAS) is being conducted in parallel with study 201584 (FLAIR) with the aim to pool data generated from the current study with study 201584, in order to evaluate key program objectives.

2. INTRODUCTION

While advances in the development of new antiretroviral therapies (ART) provide extensive insights into the management of Human immunodeficiency- (HIV)infected individuals, chronic HIV infection continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus, and issues associated with long term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires that we continue to improve on the durability, safety and tolerability, and convenience of all antiretroviral classes.

Fixed-dose combinations (FDCs) have greatly advanced HIV treatment by allowing simplification of dosing and reducing pill burden. However, adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Among regimens of comparable efficacy, physicians and HIV-1-infected patients who receive ART rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Drug resistant virus eventually emerges in most patients who struggle with consistent adherence. Different HIV treatment modalities are being developed to help improve adherence and patient outcomes, and prevent resistance and transmission of the virus.

There is also an increasing desire to develop nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens for long-term treatment of HIV infection as an approach to avoid known NRTI-associated adverse drug reactions and long-term toxicities. In addition, while there are no currently approved two-drug regimens to maintain suppression, simplifying treatment has long been a goal to increase treatment compliance and improve the quality of life for patients with HIV.

Cabotegravir (CAB) is a potent integrase inhibitor that possesses attributes that allow formulation and delivery as a long-acting (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. 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 patients.

2.1. Study Rationale

The overall objective of the CAB LA + RPV LA clinical development program is to develop a highly effective, well tolerated two drug long-acting injectable regimen which has the potential to offer improved treatment convenience, compliance and improved quality of life for individuals with HIV compared to current standard of care. 201585 (ATLAS) is being conducted to establish if human immunodeficiency virus type 1 (HIV-1) infected adult participants with current viral suppression on a regimen with 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent, remain suppressed upon switching to a two-drug intramuscular (IM) long-acting (LA) regimen of cabotegravir (CAB) and rilpivirine (RPV). This study is designed to demonstrate the non-inferior antiviral activity of switching to CAB LA 400 mg + RPV LA 600 mg every

4 weeks for 48 weeks (4 weeks oral CAB + RPV, 44 weeks LA therapy) compared to continuation of current antiretroviral therapy (current ART). This study will also provide important long-term antiviral activity, safety, tolerability and patient satisfaction data on CAB LA 400 mg + RPV LA 600 mg through at least Week 96. Additionally, participants initially randomized to continue current ART will be given an option to switch to LA therapy at Week 52. Eligible participants (HIV-1 RNA <50 c/mL at Week 48) will transition to LA dosing, beginning with 4 weeks oral CAB + RPV therapy at Week 52, and will receive the first IM CAB LA + RPV LA injections at Week 56 (See Section 6.3 for additional details).

2.2. Brief Background

It is estimated that 36.9 million people are currently living with HIV/AIDS and that the worldwide epidemic continues to grow at a rate of two million new infections and cause 1.2 million deaths per year [UNAIDS, 2015]. While advances in the development of new antiretroviral therapies (ART) provide extensive insights into the management of HIV-infected individuals, chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with long term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires a need for continuous improvement on the durability, tolerability and convenience of all antiretroviral classes.

A study by the Antiretroviral Therapy Cohort Collaboration [ART-CC, 2013] found that of more than 21,000 patients in a European and North American cohort on their first combination antiretroviral therapy (cART) regimen (either PI or NNRTI-based), 51% modified or interrupted their first cART regimen during a median of 28 months of follow-up with one third of interruptions occurring within the first 6 months of starting therapy. Forty percent of all treatment interruptions were due to the secondary side effects or toxicities of cART, 17% were due to the desire for simplification of the regimen and 14% were due to patient choice. These observations have led to numerous "switch" ART studies, designed to understand the efficacy, safety, and tolerability of switching patients from one regimen to another.

Previous studies have evaluated switches to ritonavir-boosted PI monotherapy in virologically suppressed patients [Bierman, 2009 and Arribas, 2012]. These studies suggest that simplifying from a three drug dual class regimen to a single boosted protease inhibitor may be a safe and effective option for the majority of participants studied who have effectively maintained viral suppression. In the OLE study, virologically suppressed (HIV-1 RNA <50 c/mL) HIV-1 infected participants receiving a lopinavir-ritonavir (LPV/r) + lamivudine (3TC) or emtricitabine (FTC) based NRTI regimen simplified to a dual regimen of LPV/r + 3TC or FTC. In a modified Intent-to-Treat (m-ITT) analysis, dual therapy with LPV/r + 3TC demonstrated non-inferiority efficacy and comparable safety to LPV/r + 2 NRTIs [Arribas, 2015].

Two Phase IIb studies (LAI116482 GlaxoSmithKline Document number 2014N216014_00, Study LAI116482 [LATTE] and (20056 GlaxoSmithKline Document Number 2013N168152_05, Study [LATTE-2])]) have been conducted with oral CAB

and/or intramuscular (IM) CAB LA and oral RPV and/or IM RPV LA, evaluating an induction / maintenance simplification approach. In LAI116482 (LATTE), participants were randomized to oral CAB 10, 30, or 60 mg + two nucleoside reverse transcriptase inhibitors (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 rilpivirine (RPV), and continuing on two drug ART (CAB + RPV). A robust virologic response (HIV-1 RNA <50 c/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) (GlaxoSmithKline Document Number 2014N216014_00). 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 favourably to EFV 600 mg plus 2 NRTIs (71%; ITT-E, MSD=F).

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).

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 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%]).

The 200056 study (LATTE-2) evaluated a 20 week induction of HIV-1 RNA suppression with a three drug oral antiretroviral regimen consisting of CAB + ABC / 3TC Fixed Dose Combination (FDC) followed by randomization to a two-drug two-class regimen consisting of intramuscular (IM) long-acting (LA) 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.

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.

The primary endpoint for 200056 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 intramuscular (IM) injections with CAB LA + RPV LA every 4 weeks (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. 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.

Week 48 was a secondary endpoint for 200056, 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. Although the proportion of participants with virologic success was similar for Q8W and Q4W dosing, the reason for Snapshot failure was different between the arms. There were more Snapshot failures for virologic reasons on the Q8W arm (n=8, 7%) than in the Q4W arm (n=1, <1%), and more participants with no virologic data (discontinued due to AE or other reasons) on the Q4W arm (n=9, 8%) compared to the Q8W arm (n=1, <1%).

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 delaviridine (>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).

Overall AEs and clinical chemistries were similar to those observed in prior studies with CAB, without discernible trends between Q8W, Q4W, and oral. Injections were well tolerated with two participants discontinuing due to injection tolerability through 48 weeks (both on Q8W dosing). The vast majority of injection site reactions were due to pain/discomfort with nearly all injection site reactions classified as mild (82%) or moderate (17%), with <1% of reactions classified as severe. There was no discernible tolerability difference between Q4W (2 mL) dosing and Q8W (3 mL dosing). The most common non-ISR AEs during the Maintenance Phase were nasopharyngitis (24%),

headache (16%), and diarrhea (13%) on IM arms and nasopharyngitis (30%), headache (11%), and diarrhea (5%) on oral CAB. Through Week 48, serious adverse events (SAEs) during the Maintenance Phase occurred in 7% of participants randomized to CAB LA + RPV LA and 5% of participants randomized to remain on oral treatment, none were drug related.

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.

The primary objective of this study will be to demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA compared to continuation of current first line antiretroviral regimen (current ART) over 48 weeks in HIV-1 infected antiretroviral therapy (ART)-experienced participants.

This study is being conducted in parallel with 201584 (the First Long-Acting Injectable Regimen- FLAIR study) with the aim to pool data generated from the current study with study 201584, in order to evaluate key program objectives.

3. OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
To demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of current first line antiretroviral regimen over 48 weeks in HIV-1 infected antiretroviral therapy (ART)-experienced participants	• Proportion of participants with a 'virologic failure' endpoint as per Food and Drug Administration (FDA) Snapshot algorithm at Week 48 (Intent-to-Treat Exposed [ITT-E] population).
Secondary	
To demonstrate the antiviral and immunologic activity of switching to intramuscular CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of current ART	• Proportion of participants with Plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] population). • Proportion of participants with plasma HIV-1 RNA <200 c/mL at Week 48 using the Snapshot algorithm (ITT-E population) • Proportion of participants with confirmed virologic failure (two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) at Week 48 • Absolute values and change from Baseline in plasma HIV-1 RNA (log_{10} c/mL) at Week 48. • Absolute values and change from Baseline in CD4+ lymphocyte count at Week 48 • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death over 48 Weeks
To evaluate the safety and tolerability of switching to CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of current ART	• Incidence and severity of adverse events (AEs) and laboratory abnormalities over time including Week 48 • Proportion of participants who discontinue

Objectives	**Endpoints**
	treatment due to AEs over time including Week 48 • Absolute values and changes in laboratory parameters over time including Week 48
To evaluate the effects of CAB LA + RPV LA every 4 weeks on fasting lipids over time compared to continuation of current ART over time.	• Change from Baseline in fasting lipids over time including Week 48 and Week 96.
To assess viral resistance in participants experiencing protocol-defined virologic failure	• Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV and other on-study ART at Week 48
To assess the impact of Baseline third agent treatment class (INI, NNRTI, or PI) on efficacy, safety, tolerability, and viral resistance of CAB LA + RPV LA compared to continuation of current ART	<u>By Baseline third agent treatment class:</u> • Proportion of participants with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 48 (Intent-to-Treat Exposed [ITT-E] population). • Proportion of participants with Plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm (Intent-to-Treat Exposed [ITT-E] population) • Incidence and severity of select AEs and laboratory abnormalities over time including Week 48 • Proportion of participants who discontinue treatment due to AEs over time including Week 48 • Absolute values and changes in select laboratory parameters over time including Week 48 • Incidence of observed genotypic and phenotypic resistance to current antiretroviral regimen and to CAB or RPV for participants meeting confirmed virologic failure

Objectives	**Endpoints**
To characterize CAB and RPV concentrations and population pharmacokinetics and identify important determinants of variability.	• Plasma PK parameters for CAB LA and RPV LA (when evaluable, $C_{trough,}$ concentrations post dose [~Cmax], and area under the curve [AUC]) • Demographic parameters including, but not limited to, age, sex, race, body weight, body mass index, and relevant laboratory parameters will be evaluated as potential predictors of inter- and intra-participant variability for pharmacokinetic parameters
To evaluate the antiviral and immunologic effects, safety, tolerability, and viral resistance of CAB LA + RPV LA for participants during the Extension Phase • For participants randomized to CAB LA+ RPV LA at Day 1 • For participants electing to transition to CAB LA + RPV LA in the Extension Phase	• Proportion of participants with plasma HIV-1 RNA <50 c/mL over time including week 96 (Observed Case). • Proportion of participants with confirmed virologic failure (two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) through Week 96 • Absolute values and change from Baseline in plasma HIV-1 RNA over time including Week 96 • Absolute values and changes from Baseline in CD4+ cell counts over time including Week 96 • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death) • Incidence and severity of AEs and laboratory abnormalities over time including Week 96 • Proportion of participants who discontinue treatment due to AEs over time including Week 96 • Absolute values and changes in laboratory

Objectives	**Endpoints**
	parameters over time including Week 96 • Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on study ART at Week 96
To assess the acceptance of pain and injection site reactions following injections	• Change from Week 5 in Dimension scores ("Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of iNjection questionnaire (PIN) • Proportion of participants considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the Perception of iNjection questionnaire (PIN)
To assess degree of health-related quality of life (HRQoL)	• Change from Baseline in HR QoL using the HIV/AIDS-targeted quality of life questionnaire (HAT QoL) short form at Week 24, Week 48, Week 96 (or Withdrawal).
To assess the health status	• Change from Baseline in health status at Week 24, Week 48, and Week 96 (or Withdrawal) using the 12-item Short Form Survey (SF-12). .
To assess treatment satisfaction of CAB LA + RPV LA compared to continuation of current ART	• Change from baseline in total "treatment satisfaction" score, and individual items scores of the HIVTSQs at Weeks 4b, 24, 44, 96 (or Withdrawal) • Change in treatment satisfaction over time using the HIVTSQc at Week 48 (or Withdrawal)
To assess treatment acceptance	• Change from Baseline in treatment acceptance at Week 8, Week 24, Week 48, Week 96 (or Withdrawal) using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT)

Objectives	**Endpoints**
	questionnaire
To assess tolerability of injections	• Change from Week 4b in tolerability of injection at Week 5, Week 40, Week 41, and Week 96 using the Numeric Rating Scale (NRS) within the CAB + RPV LA arm.
Exploratory	
To explore the effect of patient characteristics (e.g., demographic factors, Baseline CD4+) on the virologic and immunologic responses to CAB LA+ RPV LA compared to continuation of current ART	• Proportion of participants by patient subgroup(s) (e.g., by age, gender, BMI, race, HIV-1 subtype, Baseline CD4+) with Virologic Failure over time including Week 48 using the Snapshot algorithm for the ITT-E population • Proportion of participants by patient subgroup(s) (e.g., by age, gender, body mass index (BMI), race, HIV-1 subtype, Baseline CD4+) with plasma HIV-1 RNA <50 c/mL over time including Week 48 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ cell counts by subgroups at Week 48
To explore relationship(s) between plasma concentrations of CAB and RPV and pharmacodynamic endpoints.	• Relationship between plasma PK concentrations and virologic, immunologic responses, and/or occurrence of adverse events [AEs] over time may be explored.
To evaluate renal and bone biomarkers in participants treated with CAB LA + RPV LA compared to continuation of current ART	• Absolute value and change from Baseline in renal (in urine and blood), and bone (in blood) over time
To assess preference for CAB LA+ RPV LA compared to oral ARV using a single dichotomous preference question.	• For patients randomized to the “CAB LA + RPV LA” arm, preference for CAB LA + RPV LA compared to oral ARV regimen, at Week 48 • For patients randomized to the “Current ART” arm who switched to the injectable treatment, preference for CAB LA + RPV LA compared to current ART regimen at Week 96 (end of extension phase- secondary

Objectives	Endpoints
	analysis)
To assess reason for switching using a single question.	• The reasons for willingness to switch ART at baseline and for patients randomized to the "Current ART" arm at Week 52.

4. STUDY DESIGN

4.1. Overall Design

201585 (ATLAS) is a Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of a two drug regimen of CAB LA + RPV LA compared with maintenance of current ART. Approximately 570 adult HIV-1 infected patients who are on a stable ARV regimen containing 2 NRTIs plus an INI, NNRTI, or a PI will be randomized 1:1 to continue current ART or be switched to the CAB LA + RPV LA regimen through 52 weeks. The study will continue with an Extension Phase up to at least 96 weeks.

Participants will be randomized (1:1) at Day 1 to either continue on current ART or to discontinue current ART and begin oral therapy with CAB 30 mg + RPV 25 mg once daily to determine individual safety and tolerability, prior to administration of CAB LA + RPV LA. Current ART dosing on Day 1 is recommended to occur after randomization to avoid overlap of regimens (in the event that the participant is assigned to the CAB LA + RPV LA treatment arm). However, if the participant takes current ART prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1.

For those randomized to receive CAB + RPV, at the Week 4a visit safety assessments (including e.g., clinical chemistries) will be performed as per the Time and Events Table (Section 7.1). At visit Week 4b, participants will return to the clinic, take the last dose of oral CAB + RPV, and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). The first injection visit (Week 4b) can be performed once central lab results are available and safety parameters are reviewed. If a retest is required based on Week 4a labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 4a). Participants will remain on oral CAB 30 mg + RPV 25 mg until the Week 4b injection visit, and until any required Visit 4a retest results are available for review. The visit schedule following the oral lead-in phase will be based on timing of the first injection visit at Week 4b such that the Week 5 visit should be performed approximately 7 days after the Week 4b visit.

Participants who are randomized to continue current ART and successfully complete Week 48 (without meeting study defined withdrawal criteria and remain virologically suppressed: HIV-1 RNA <50 c/mL) will be given the option at Week 52 to switch to the LA arm in the Extension Phase or be withdrawn from the study.

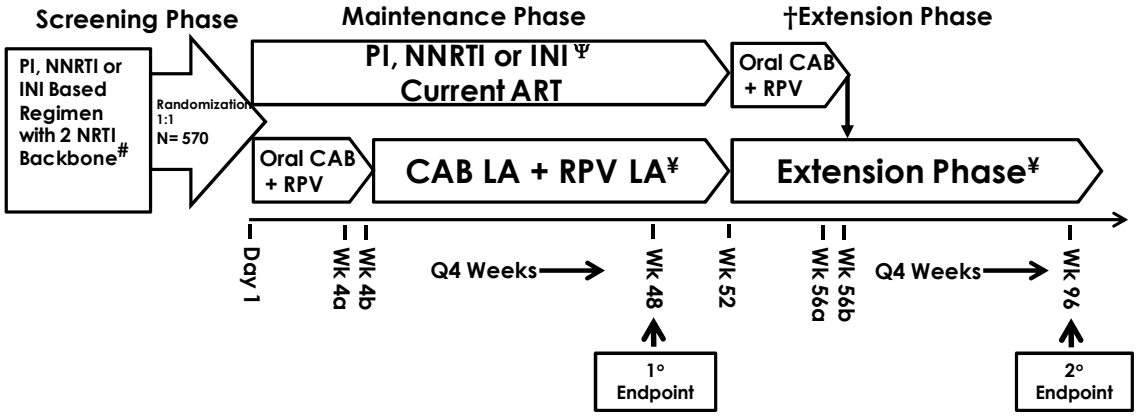
Randomization will be stratified by baseline third agent class (PI, INI, or NNRTI), and gender at birth. The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48. The proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] population) is a key secondary endpoint.

The sample size of 285 per arm is such that the study has approximately 97% power to demonstrate non-inferiority in the proportion of participants with snasphot virologic failure at Week 48 using a 6% margin, assuming a true 3% failure rate for CAB LA + RPV LA and a 2% failure rate for the current ART control arm and using a 2.5% one-sided alpha level. This sample size is primarily chosen so that the pooled analysis of data from this study and study 201584 (combined sample size of 570 per arm) will have 90% power to show non-inferiority for the proportion of participants with Snapshot virologic failure at Week 48 using a 4% non-inferiority margin, under the assumptions described above.The randomized portion of the study will continue for 52 weeks with an Extension Phase up to at least 96 weeks

An Independent Data Monitoring Committee (IDMC) will evaluate interim efficacy, tolerability, safety and PK of CAB LA + RPV LA at predefined times during the study. An interim futility analysis will be performed for the IDMC with the intent of having approximately 50% of participants reaching Week 24 with the intent to complete this analysis prior to any participants transitioning to the Extension Phase at Week 52. In addition, an ad hoc IDMC review of safety and efficacy data would also be triggered if the number of virologic failures exceeds pre-specified thresholds as per the IDMC charter. In addition, the IDMC may also monitor the incidence of participants meeting PDVF criteria through Week 48 to ensure that participants are not being sub-optimally treated in the CAB LA + RPV LA arm. Additional details are provided in Section 9.3.2.4, and in the IDMC charter, which is available upon request.

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during this study, except those allowed and defined in the protocol. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be communicated promptly to the study medical monitor.

Figure 1 201585 (ATLAS) Study Schematic



N=570, randomized 1:1 to each arm and stratified by baseline 3rd Agent class and gender at birth.
# Must be on uninterrupted current regimen (either the initial or second cART regimen) for at least 6 months prior to Screening (See Section 5.1 and Section 5.2). Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening. No history of virologic failure. No evidence of viral resistance based on the presence of any resistance-associated major INI, or NNRTI mutation (except K103N) from prior genotype assay results. No current or prior history of etravirine use.
ΨINI based regimen excludes abacavir/dolutegravir/lamivudine (TRIUMEQ), and INI therapy will be capped at approximately 40% of study enrolment for current ART
†Optional Extension Phase to CAB LA + RPV LA at Wk 52 for participants randomized to current ART
¥Participants who withdraw from IM arm must go into 52 week long term follow up phase

4.2. Treatment Arms and Duration

4.2.1. Screening Phase (Up to 35 days)

Informed consent must be obtained prior to any study procedures, including any Screening assessment.

Participants will complete a screening period of up to 35 days. A single repeat of a procedure/lab parameter is allowed to determine eligibility (unless otherwise specified). In exceptional circumstances only, if a repeat lab is required because a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor for consideration of participant eligibility. A repeat central lab will be submitted concurrently or at the next planned visit. Participants may be re-screened once which requires a new participant number. Participants who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be randomized as soon as all eligibility requirements have been confirmed at the site.

4.2.2. Maintenance Phase (Day 1 up to Week 52)

At Day 1, Eligible participants will be randomized 1:1 to either:

- Oral CAB 30 mg + RPV 25 mg once daily for four weeks (participants will be assessed for safety and tolerability after four weeks). At Week 4a, participants

will have the assessments completed as per the Time and Events Table (Section 7.1.), including clinical chemistries. At visit Week 4b, the participant will return to the clinic to take the last dose of oral CAB + RPV, and to receive the first CAB LA + RPV LA injections (within 2 hours of the final oral dose). The first injection visit with IM CAB LA 600 mg and RPV LA 900 mg (Week 4b) can be performed once central lab results are available and safety parameters are reviewed. The second and third IM injections with CAB LA 400 mg and RPV LA 600 mg will be performed at Week 8 and Week 12. There will be a one week dosing window for the second and third IM injections such that the second injection occurs within the window of Week 7 and Week 8 but no later than Week 8 and the third injection occurs within the window of Week 11 and Week 12 but no later than Week 12. Subsequent injections with CAB LA 400 mg and RPV LA 600 mg will occur every 4 weeks thereafter (±7 days from the visit schedule allowed but not preferred). In addition, starting after the Week 12 injection, efforts should be made to limit time between injection visits to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds or is projected to exceed 5 weeks.

OR

- Continue on current ART regimen for 52 weeks. Participants who successfully complete Week 52 (without meeting study defined withdrawal criteria and who remain virologically suppressed: HIV-1 RNA <50 c/mL) will be given the option to switch to the LA arm in the Extension Phase or be withdrawn from the study.

If in the opinion of the Investigator, a participant experiences a significant safety event while taking oral CAB or RPV, administration of the first injections will be determined ONLY in consultation with the Medical Monitor. Any rash that is possibly related to study drug, and is present during the CAB + RPV oral lead-in period, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA (See Section 7.4.4.13).

Randomization will be stratified by baseline third agent class (INI, NNRTI, or PI), and gender at birth.

CAB + RPV oral, CAB LA + RPV LA IM, and current ART will be administered in an open-label fashion throughout the study. For participants randomized to the current ART arm, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their current ART during the Maintenance Phase.

The primary endpoint analysis of the proportion of participants with snapshot virologic failure and the key secondary endpoint analysis of the proportion of participants with plasma HIV-1 RNA <50 copies per milliliter (c/mL), both defined according to the FDA Snapshot algorithm for the Intent-to-treat exposed (ITT-E) population, will occur at Week 48. The study will continue through the Extension Phase, enabling longer-term evaluation of CAB+ RPV on measurements of efficacy, safety, and tolerability.

Following the Week 48 primary endpoint visit, participants randomized to current ART electing to participate in the Extension Phase will stay on their current ART regimen until

Week 52 to ensure availability of results from the Week 48 HIV-1 RNA testing. A single repeat of HIV-1 RNA for any participant with a HIV-1 RNA ≥50 c/mL and < 400 c/mL at Week 48 must be performed. The retest should be scheduled as soon as possible (but no later than 4 weeks from the Week 48 visit). As per the snapshot algorithm, if the retest HIV-1 RNA is <50 c/mL then the participant will be considered to have met the secondary endpoint of virologic responder by FDA's Snapshot algorithm at Week 48. If the retest HIV-1 RNA is ≥50 c/mL then the participant will be considered to be a virologic non-responder at Week 48.

4.2.3. Extension Phase

4.2.3.1. Participants Entering from the CAB LA + RPV LA Arm

All participants who successfully complete 52 weeks of CAB LA + RPV LA treatment in the Maintenance Phase will continue to have access to both CAB LA and RPV LA in the Extension Phase until study treatment is either locally approved and commercially available (including through local public/government health sectors), the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 4 weeks as per the Time and Events Schedule (Section 7.1)

4.2.3.2. Participants Entering from the current ART ARM

Participants randomized to continue current ART will have the option to either continue study participation by switching to CAB LA + RPV LA in the Extension Phase, or to complete their study participation at Week 52 (no withdrawal visit needed).

Participants who choose to continue on to the Extension Phase will need to be assessed for eligibility to begin the CAB LA + RPV LA regimen. Participants will continue on their current ART Maintenance regimen while eligibility is being confirmed. All participants with an undetectable HIV-1 RNA (<50 c/mL) result from the Week 48 visit are eligible to enter the Extension Phase. A single repeat of HIV-1 RNA for any participant with a HIV-1 RNA ≥50 c/mL and < 400 c/mL at Week 48 must be performed. The retest should be scheduled as soon as possible (but no later than 4 weeks from the Week 48 visit). Participants with HIV-1 RNA <50 c/mL upon retest are eligible to enter the Extension Phase. Participants with HIV-1 RNA ≥400 c/mL at Week 48 are not eligible to enter the Extension Phase, will not be allowed a repeat to determine eligibility, and will therefore be withdrawn from the study.

Eligibility and Participant Management for entry into Extension Phase (Current ART ARM)	
Result of HIV-1 RNA at Week 48	**Action**
<50 c/mL	Begin Extension Phase with Oral CAB + Oral RPV at Week 52
≥50 c/mL but <400 c/mL	Perform HIV-1 RNA retest as soon as possible (not later than 4 weeks).
• Single repeat <50 c/mL	Begin Extension Phase with Oral CAB + Oral RPV at Week 52
• Single repeat ≥50 c/mL	Cannot begin Extension Phase and must be withdrawn from study; Complete Week 52 visit (no additional withdrawal visit required)
≥400 c/mL	Cannot begin Extension Phase and must be withdrawn from study; Complete Week 52 visit (no additional withdrawal visit required)

Participants with a Week 48 HIV-1 RNA <50 c/mL, will initiate a 4 week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily at Week 52. Clinical chemistries will also be assessed. At Week 56a, following the 4 week CAB + RPV oral lead-in, participants will have additional safety assessments including clinical chemistries as per the Time and Events Table (Section 7.1). In addition, central lab results and safety parameters from the Week 56a visit must be available and reviewed before the Week 56b visit. If a clinical chemistry retest is required base on the Week 56a labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 56a). Participants will remain on oral CAB 30 mg + RPV 25 mg until the Week 56b injection visit, and until any required Visit 56a retest results are available for review.

At visit Week 56b, participants will return to the clinic, take the last dose of oral CAB + RPV, and receive the first CAB LA + RPV LA injections (within 2 hours of the final oral dose of CAB + RPV). The Week 56b visit can be performed as soon as central lab results from the Week 56a visit become available and safety parameters are reviewed. If a retest is required based on Week 56a labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 56a) Participants will remain on oral CAB 30 mg + RPV 25 mg until the Week 56b injection visit, and until any required Visit 56a retest results are available for review. The visit schedule for the Extension Phase following the oral lead-in phase will be based on timing of the first injection visit at Week 56b. The second and third IM injections with CAB LA 400 mg and RPV LA 600 mg will be performed at Week 60 and Week 64. There will be a one

week dosing window for the second and third IM injections such that the second injection occurs within the window of Week 59 and Week 60 but no later than Week 60 and the third injection occurs within the window of Week 63 and Week 64 but no later than Week 64. Subsequent injections with CAB LA 400 mg and RPV LA 600 mg will occur every 4 weeks thereafter with a two-week dosing window (±7 days from the visit schedule allowed but not preferred). Starting after the Week 64 injection, the interval between injection visits should be limited to a maximum of 5 weeks. Following the Week 64 injection, the interval between injection visits should be limited to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds or is projected to exceed 5 weeks.

Additionalanalyses including safety and efficacy endpoints will be based on Week 96 data. A single repeat of HIV-1 RNA for any participant with a HIV-1 RNA ≥50 c/mL and < 400 c/mL at Week 96 must be performed. The retest should be scheduled as soon as possible (but no later than 4 weeks from the Week 96 visit.

Participants will continue study treatment in the Extension Phase until CAB LA and RPV LA are either locally approved and commercially available (including through local public/government health sectors), the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 4 weeks. See the Time and Events Table (Section 7.1) for more information.

Participants not eligible to enter the Extension Phase will end their study participation (Week 52 will be the last study visit, no withdraw visit needed). Sites may be reimbursed for up to a one month supply of antiretroviral medication to facilitate transition to non-study ART for participants that do not qualify for the Extension Phase.

4.2.4. Long-Term Follow-Up (LTFU) Phase – IM Regimen Only

Any participant who receives at least a single dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent the potential selection of INI- and/or NNRTI-resistant mutants.

Investigators must discuss the choice of the follow-up HAART regimen with the Medical Monitor prior to initiating the new regimen with the participant. HAART therapy should be initiated within 4 weeks of the last injection

The LTFU will begin the day of the last CAB LA and/or RPV LA dose and continue for 52 weeks, or until CAB LA + RPV LA is locally approved and commercially available . These participants will not complete a Withdrawal visit, but will instead move directly into the Long-Term Follow-Up Phase as per the Time and Events Schedule.

Participants will be assessed with clinic visits at months 1, 3, 6, 9 and 12 during the Follow-Up Phase. Female participants of child bearing potential must continue to use adequate contraception methods (see Study Procedures Manual [SPM] for list of accepted forms of contraception) for at least 52 weeks after the last injection.

In order to assure that participants have access to HAART during the Long-Term Follow-Up Phase, GSK may supply HAART regionally or reimbursement will be provided as needed during this phase. As participants approach the end of the Long-Term Follow-Up Phase (e.g., Prior to Month 12 visit), investigative sites and/or participants must make alternative arrangements for independent access of the participant's continued HAART off / post study.

The Long-Term Follow-Up Phase may be shortened at any time during the study for various reasons; e.g., better understanding of risks of development of resistance as CAB and RPV exposures decline, regulatory approval and commercial availability, end of study timings, etc.

This phase is considered study participation and participants will be followed on study during this time. A withdrawal visit is not required for participants who do not complete the Long-Term Follow-Up Phase. The participants' last on study visit will be considered as their withdrawal visit.

4.2.5. Dose Modifications

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during the study. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements is essential and required for study conduct.

In exceptional circumstances, and in consultation with the Medical Monitor, Investigators may provide oral CAB and/or RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. Should a participant need "oral bridging", sites must contact the Medical Monitor for guidance on treatment strategies prior to a missed CAB LA + RPV LA dose. Should a participant not notify the site in advance, the Medical Monitor must be contacted for further treatment guidance. See Section 6.8.1 for additional information on oral bridging.

4.3. 207966 (ATLAS-2M) Rollover Option

The 207966 (ATLAS-2M) study is being conducted in approximately 1020 participants to establish if human immunodeficiency virus type 1 (HIV-1) infected adults with current viral suppression (HIV-1 RNA <50 c/mL) remain suppressed upon administration of a two-drug intramuscular (IM) long-acting (LA) regimen of cabotegravir (CAB) and rilpivirine (RPV) administered every 8 weeks (Q8W; every 2 months). The ATLAS-2M study is designed to demonstrate the non-inferior antiviral activity of CAB LA 600 mg + RPV LA 900 mg administered every 8 weeks compared with CAB LA 400 mg + RPV LA 600 mg administered every 4 weeks (Q4W; monthly) over a 48-week treatment period. ATLAS-2M will also provide comparative data on antiviral activity, safety, tolerability, and patient satisfaction through Week 96. It is anticipated that the majority of ATLAS participants will transition to the ATLAS-2M study

Upon local approval and implementation of the ATLAS-2M trial, investigators will approach all potentially eligible ATLAS participants with the optional consent for ATLAS-2M participation and potential randomization to the CAB LA + RPV LA Q4W

or Q8W regimen. If a participant cannot or chooses not to transition to the ATLAS-2M trial, or is otherwise determined to be ineligible for ATLAS-2M, the participant can elect to continue participation in ATLAS trial without limitations and according to the approved protocol design.

Eligibility to transition to ATLAS-2M at Week 52 (at the earliest) will be determined once the final central lab results from ATLAS, following (at minimum) completion of the ATLAS Week 48 visit are available and safety parameters have been reviewed. Separate Screening Labs will be utilized to inform eligibility for ATLAS-2M; however, in some occasions and upon consultation with the Medical Monitor, individual lab results and safety data from the final visit of the ATLAS study can be considered towards informing eligibility for the ATLAS-2M study as long as all other screening and eligibility criteria are met.

4.3.1. 201585 (ATLAS) to 207966 (ATLAS-2M) Transition Strategy

Upon the final ATLAS on-study visit (ATLAS Week 52 or later), which overlaps with the Day 1 Baseline visit for ATLAS-2M, all procedures and assessments must be performed and recorded as per both individual study Time and Events Tables with the exception that participants will receive only the scheduled Day 1 ATLAS-2M treatment (participants will not receive the corresponding ATLAS study treatment).

ATLAS participants on current ART therapy who transition to ATLAS-2M at the ATLAS Week 52 visit, will begin a 4 week oral lead-in treatment with CAB 30 mg + RPV 25 mg once daily, per the ATLAS-2M Time and Events table. Participants currently receiving CAB LA + RPV LA Q4W at the overlapping visit (including those who were originally randomized to the Q4W regimen and those who more recently switched to the Q4W regimen within the Extension Phase of ATLAS) will continue CAB LA + RPV LA Q4W or initiate CAB LA + RPV LA Q8W treatment as per the ATLAS-2M randomized treatment schedule.

Following the baseline Day 1 visit for ATLAS-2M, participants will follow all schedules and activities of the ATLAS-2M trial. No withdrawal visit nor long-term follow up phase participation for ATLAS is required. An in-clinic Follow-Up visit (which may or may not overlap with an ATLAS-2M visit) will be conducted approximately 4 weeks after the last dose of ATLAS study medication for participants with ongoing AEs, and serious adverse events (SAEs) related & not related to study drug and any laboratory abnormalities that are considered to be AEs or clinically significant at the last ATLAS on-study visit.

Transition from the ATLAS CAB LA + RPV LA Q4W Arm:

Participants originally randomized to the CAB LA + RPV LA Q4W arm in ATLAS and who are eligible for the ATLAS-2M trial can transition to ATLAS-2M upon completion of the ATLAS Week 52 primary endpoint or can continue ATLAS participation in the Extension Phase, until Study ATLAS-2M has been locally approved/implemented and eligibility for the ATLAS-2M trial has been confirmed.

Transition from the ATLAS current ART Arm:

Participants originally randomized to the current ART Arm in ATLAS will have the following options to transition to ALTAS-2M:

At Week 52 Visit

- Transition directly from current ART therapy in ATLAS at Week 52 to randomization at Day 1 in ATLAS-2M

After Week 52 Visit

- Transition from current ART therapy to oral CAB + Oral RPV lead-in treatment followed by CAB LA + RPV LA Q4W within the ATLAS Extension Phase and transition to ATLAS-2M at a subsequent visit. This option may be employed in the event that the ATLAS-2M study is not approved/implemented locally by the time a participant reaches the Week 52 visit (Extension Phase) of ATLAS or a decision to transition to ATLAS-2M is made following the transition to the Extension Phase.

Additional details of the ATLAS-2M study design, eligibility requirements, and transition guidance can be referenced within the current version of the ATLAS-2M protocol.

4.4. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will evaluate the efficacy, tolerability, safety, and PK of the treatment regimens. An interim analysis will be performed for the IDMC to evaluate the efficacy of CAB LA + RPV LA prior to the final analysis. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

An interim futility analysis will be performed with the intent of having approximately 50% of participants reaching Week 24 and providing sufficient lead time to allow the IDMC to review the data prior to any participants reaching the Week 48 visit. A futility rule based on Bayesian posterior predictive probability approach will be applied to assess the probability that CAB LA + RPV LA injectable regimen demonstrate non-inferiority to the continued current ART arm given the partial data set. The sponsor will remain blinded to this analysis.

In addition, the IDMC may also monitor the incidence of participants meeting CVF criteria through Week 48 to ensure that participants are not being sub-optimally treated in the CAB + RPV arm.

Full details of the analyses, estimated timing and the decision criteria that will be used to determine regimen performance will be pre-specified in the IDMC Charter.

4.5. Type and Number of Participants

The target population to be enrolled is virologically suppressed participants with HIV-1 infection on stable antiretroviral therapy (ART).

Assuming 30% screen failure rate, approximately 815 HIV-1-infected adult participants will be screened to achieve 570 randomized participants for a total of 285 participants per treatment group. Participants will be enrolled from multiple countries which may include Argentina, Australia, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the United States.

Randomization will be stratified by baseline third agent class (PI, INI, or NNRTI) and gender at birth. 201585 (ATLAS) will exclude enrolment of participants treated with abacavir/dolutegravir/lamivudine (TRIUMEQ) and will aim to limit enrolment of participants on an INI to approximately 40%. TRIUMEQ comparator data for the CAB LA + RPV LA program will be generated from study 201584 (FLAIR) and will be included within a planned pooled analysis with 201585 (ATLAS) results. A goal of this study is to enrol populations who are underrepresented in clinical studies including approximately 25% women. To provide sufficient data to determine whether either gender is correlated with treatment response, sites are expected to take into account gender in their screening strategies. Enrolment may be allowed to continue at select sites in order to reach targets in these key study populations.

4.6. Design Justification

The design of this study (1:1 randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study) is well established for confirming the non inferiority of an investigational agent compared with an active comparator and is generally accepted by regulatory authorities as rigorous proof of antiviral activity. The primary endpoint, proportion of participants defined as virologic failures by the FDA Snapshot algorithm is recommended in the FDA's 2015 guidance document (FDA, 2015) for assessing efficacy in Switch Trials. The key secondary endpoint, proportion with plasma HIV-1 RNA <50 c/mL at Week 48, is also a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression. The Extension Phase will allow for a collection of both additional data for participants switching from current ART to CAB LA + RPV LA, as well as longer term efficacy, safety and tolerability data from participants randomized to CAB LA + RPV LA during the Maintenance Phase.

Various approaches to simplify a patient's antiretroviral therapy (ART) regimen, after achieving viral suppression, have been studied. Previous studies have evaluated switches to ritonavir-boosted PI monotherapy therapy in virologically suppressed patients [Bierman, 2009 and Arribas, 2012]. While the data from these studies have shown both long-term non-inferiority and inferiority to continual Highly Active Antiretroviral Therapy (HAART), they suggest that simplifying from a three drug dual class regimen to a single boosted protease inhibitor may be a safe and effective option for the majority of participants studied who have effectively maintained viral suppression.

The 200056 (LATTE-2) (GlaxoSmithKline Document Number 2013N168152_05) clinical trial evaluated a different simplification approach and served as proof of concept for 201585. In 200056, HIV-1 RNA suppression was induced with a three drug antiretroviral regimen consisting of CAB + ABC/3TC FDC, and then participants switched to a two-drug two-class regimen consisting of CAB LA + RPV LA for the maintenance of HIV-1 RNA suppression. Results demonstrate that through 32 weeks on

two-drug maintenance therapy, 95% (Q8W) and 94% (Q4W) of participants on injectable dosing were virologic successes by snapshot, compared to 91% of participants continuing three drug oral CAB + NRTIs, meeting pre-specified criteria for comparability between the dosing arms. By Week 48, Q4W and Q8W arms continued to demonstrate similar efficacy (see Section 2 "Introduction" for further details). On the basis of this 200056 data, Q4W dosing was selected to progress into Phase 3 for further clinical development.

Several studies recently conducted have demonstrated the value/feasibility of a switch study design, an approach that has been shown to generate valuable data supporting ARV combinations that allow dosing flexibility, reduced toxicity and/or drug interactions or a reduction in pill burden. An injectable ART regimen may also contribute to increased medication adherence and reduced HIV transmission. A potential disadvantage of a switch study design is that effective, well-tolerated ART is discontinued at the time of switching to the simplified regimen [Carr, 2012].

The open-label design best suits the objectives of this study. A double-dummy design could not be undertaken given the diversity of the comparator regimens, and the logistical challenges of providing blinding for each regimen, along with the marked increase in pill burden that would result from this blinding. This marked increase in pill burden could both substantially hinder compliance, and discourage participant enrolment. Therefore, the value of blinding the CAB LA + RPV LA injectable regimen would be limited, relative to the burden of participants in the current ART arm receiving Q4 weekly IM injections for the duration of the study. Participants receiving placebo injections who believe that they are receiving LA injections might become less compliant with oral medication and increase risk taking behaviours. A reduction in medication adherence in turn could lead to risk of regimen failure and potential virologic resistance impacting future treatment options. Elevated risk taking could increase opportunities for virus transmission to uninfected partners. The additional risk of inadvertent non-adherence to oral ART outweighs any benefits that may be gained through a blinded design.

Importantly, a key objective for the planned Phase 3 studies is to understand the acceptability and patient reported preferences to this novel injectable regimen, relative to daily oral standard of care (SOC) ART. An unblinded study design supports collection of participant preference data in a way that would not be possible if a double-blind, double-dummy design were implemented.

Due to the complexities, limitations and risks of blinding each switch study, both Phase 3 switch studies (201585-ATLAS and 201584-FLAIR) are planned as open label studies.

4.7. Dose Justification

4.7.1. Oral Lead-In Phase

During the oral lead-in phase of this study, oral formulations of CAB and RPV will be co-administered to confirm tolerability in each participant prior to possible IM dosing with CAB LA and RPV LA. Data from study LAI116181 [GlaxoSmithKline Document Number 2011N130484_00] have demonstrated that there is no clinically relevant drug-drug interaction following repeat oral administration of CAB with RPV. The combination of oral RPV (25 mg once daily) and CAB (10, 30 or 60 mg once daily) has

been administered to HIV-infected participants in both Study LAI116482 LATTE and Study 200056 LATTE-2 (oral lead-in). In the present study, the approved recommended dose of RPV 25 mg once daily will be used in combination with CAB 30 mg once daily. The oral dose of CAB was selected based on observed safety and efficacy from the Phase 2b study 200056 LATTE study.

CAB has demonstrated good short-term safety/tolerability and antiviral activity as monotherapy following oral administration of 5 mg and 30 mg once daily. LAI116482 (LATTE) is an ongoing Phase IIb, dose-ranging study (randomized 1:1:1: to CAB 10 mg, 30 mg, or 60 mg) evaluating the long-term efficacy and safety of a two-drug, two-class, once daily combination of CAB + RPV in HIV-infected, treatment-naïve adult participants. Following a 24-week phase of induction of virologic suppression using CAB + 2 NRTIs, the regimen was simplified to oral CAB + RPV once daily for an additional 72-weeks (total comparative study duration of 96 weeks). The results of this study also informed the Phase IIb study 200056 (LATTE-2) with intramuscular CAB LA and RPV LA.

Comparable efficacy, safety and tolerability were observed across all three CAB doses at the early dose selection and confirmation visits at Week 16 and 24 in LATTE. Additionally, the proportion of participants who achieved the primary endpoint of HIV-1 RNA <50 c/mL (Missing, Switch, Discontinuation=Failure [MSDF] algorithm) at Week 48 (24 weeks on Maintenance) remained consistently high across the CAB dose arms (≥80%) with a low rate of confirmed virologic failure (Table 1). Across all dose arms, CAB achieved similar efficacy at Week 24 of Induction when co-administered with 2 NRTIs and at Week 96 when co-administered with RPV 25 mg once daily (72 weeks on Maintenance). Rates of virologic suppression through Week 96 (Maintenance) on the two drug regimen remained similar to that attained through Week 24 (Induction) on three-drug ART.

Table 1 Proportion (95% CI) of Participants with Plasma HIV-1 RNA <50 c/mL at Key Visits - Snapshot (MSDF) Analysis (ITT-E Population) in LATTE

Visit		CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	CAB Subtotal N=181	EFV 600 mg N=47
Week 16	n (%)	**54 (90)**	50 (83)	53 (87)	157 (87)	46 (74)
	95%CI Proportion	**(82, 98)**	(74, 93)	(78, 95)	(82, 92)	(63, 85)
Week 24	n (%)	**52 (87)**	51 (85)	53 (87)	156 (86)	46 (74)
	95%CI Proportion	**(78, 95)**	(76, 94)	(78, 95)	(81, 91)	(63, 85)
Week 48	n (%)	48 (80)	48 (80)	53 (87)	149 (82)	44 (71)
	95%CI Proportion	(70, 90)	(70, 90)	(78, 95)	(77, 88)	(60, 82)

CAB was administered with 2 NRTIs during the 24 week induction Phase of LATTE.

95% CIs are normal approximation confidence intervals.

CAB was well tolerated across all doses studied and none of the doses met pre-defined safety stopping criteria. A good safety and tolerability profile with a low discontinuation rate due to AEs was observed in all three dose arms with no significant dose-dependent trends in safety parameters.

Although CAB 30 mg was already selected based on short-term efficacy and safety through Week 24, the observed durability of viral suppression through 96 weeks, across all doses, provides further support for selection of the CAB 30 mg dose for Phase 3. In addition, the 30 mg dose achieves trough CAB plasma concentrations that are greater than mean CAB plasma concentrations observed following CAB LA dosing which allows an adequate assessment of safety and tolerability prior to transitioning to the long-acting, Maintenance Phase of the study.

CAB has low risk of causing or being a victim of drug-drug interactions, and therefore, the selected 30 mg dose can be safely used with most common concomitant medications without dose adjustment. CAB exposures are not impacted by the presence of food; however, given that it will be co-administered with RPV which requires food for optimal absorption, the recommended intake of oral CAB in the Phase 3 studies is with food at the same time as RPV.

Overall, the efficacy and safety data from the LATTE study, CAB LA dose simulations detailed in Section 4.7.2, and limited drug-drug interaction potential, support selection of the CAB 30 mg dose for once daily administration with the recommended approved dose of RPV 25 mg once daily during the oral lead-in phase of this study.

4.7.2. Long Acting Injectable for Maintenance Phase

During the Maintenance and Extension Phases of this study, CAB LA and RPV LA will be co-administered as two separate IM injections at each dosing visit. A CAB LA and RPV LA 4-weekly dosing regimen has been selected for evaluation in Phase 3.

The safety and efficacy of a 2-drug regimen with CAB and RPV for maintenance of virologic suppression was established in LATTE, as detailed in Section 4.7.1, and informed the Phase 2b study (LATTE-2) with CAB LA and RPV LA. Study 200056 (LATTE-2) is an ongoing, Phase 2b dose-ranging study evaluating the long-term efficacy and safety of a two-drug, two-class combination of CAB LA + RPV LA given every 4 weeks (Q4W) or every 8 weeks (Q8W), as compared to an oral three-drug regimen, for maintenance of virologic suppression in HIV-infected, treatment-naive adults. The first phase of the LATTE-2 study was a 20 week Induction Phase (16 weeks of oral CAB + 2 NRTIs, 4 weeks of CAB + 2 NRTIs + oral RPV). Participants who were eligible to continue into the Maintenance Phase were then randomized (2:2:1) to receive IM injections of CAB LA every 4 weeks (800 mg Day 1 then 400 mg Q4W) or every 8 weeks (800 mg Day 1, 600 mg Week 4, 600 mg Week 8, then 600 mg Q8W) in combination with IM RPV LA every 4 weeks (600 mg Day 1 then 600 mg Q4W) or every 8 weeks (900 mg Day 1, 900 mg Week 8, then 900 mg Q8W), respectively, or to continue on their triple ART regimen.

The Q4W dosing strategy was selected for further investigation in Phase 3 based on the efficacy, safety and tolerability at Week48, and compared to oral. Thus, the results from LATTE-2 provide the basis for the LA dosing strategy in the present study.

The proportion of participants who achieved the primary endpoint of HIV-1 RNA <50 c/mL (Missing, Switch, Discontinuation=Failure [MSDF] algorithm) by Week 32 was consistently high across both Q4W and Q8W dosing strategies (≥94%) with one participant, randomized to the Q8W regimen and one participant in the oral treatment arm with protocol-defined virologic failure during LA therapy. At Week 32, snapshot failure rate was 4% (n=5) for the Q8W Arm and <1% (n=1) for the Q4W Arm. Although the snapshot success rate at Week 48 was similar between treatment arms, the rate of snapshot failures at Week 48 increased to 7% (n=8) for the Q8W Arm but remained at <1% (n=1) for the Q4W Arm (Table 2). Refer to Section 2.2 for additional information on LATTE-2 data.

Table 2 Proportion (95% CI) of Participants with Plasma HIV-1 RNA <50 c/mL at Week 48 - Snapshot (MSDF) Analysis (ITT-E Population) in LATTE-2

Outcome	Q8W IM N=115 n (%)	Q4W IM N=115 n (%)	Q8W+Q4W N=230 n (%)	CAB 30 mg N=56 n (%)
Virologic Success, n (%)	106 (92)	105 (91)	211 (92)	50 (89)
Virologic Failure, n (%)	8 (7)	1 (<1)	9 (4)	1 (2)
Data in window not below threshold	6 (5)	1 (<1)	7 (3)	0
Discontinued for lack of efficacy	1 (<1)	0	1 (<1)	1 (2)
Discontinued for other reason while not below threshold	1 (<1)	0	1 (<1)	0
No Virologic Data	1 (<1)	9 (8)	10 (4)	5 (9)
Discontinued due to AE or Death	0	6 (5)	6 (3)	2 (4)
Discontinued for Other Reasons	1 (<1)	3 (3)	4 (2)	3 (5)

CAB LA and RPV LA were both well tolerated resulting in a low discontinuation rate due to AEs, including injection site reaction (ISR) related AEs, with no significant trends in safety parameters in either the Q8W or Q4W dosing regimens.

Due to the increased Snapshot failure rate at Week 48 for the Q8W Arm, a Q4W dosing strategy was selected for further evaluation in Phase 3. To allow some flexibility, with the exception of Week 8 and Week 12, a one-week window (on each side) around the 4-weekly dosing regimen can be allowed following Week 12 (third injection), without anticipated impact on the safety or efficacy of the regimen. For Week 8 and Week 12, there is only a minus one week window such that injections should be administered no later than Week 8 and Week 12.

For CAB LA, steady-state mean CAB pre-dose concentrations following Q4W dosing remain between the oral CAB 10 mg and 30 mg once daily mean trough concentrations, which were both doses found to be safe and efficacious in the LATTE study. For RPV LA, steady-state mean RPV pre-dose concentrations following Q4W dosing are comparable with the range of exposures following oral RPV 25 mg once daily observed to be safe and efficacious in pivotal Phase 3 studies. Maintenance Phase PK data in LATTE 2 are summarized for both regimens of CAB LA (Table 3, Figure 2) and RPV LA (Table 4, Figure 3).

Table 3 Summary of Observed PK Parameters following Repeat Dose Administration of Cabotegravir LA to HIV-infected Participants (LATTE-2)

Cohort	Plasma CAB PK Parameter[a]							
	AUC(0-τ)[b] (μg.h/mL)		Cmax[c] (μg/mL)		Individual Average C0[d] (μg/mL)		tmax[e] (d)	
	Week 24	Week 40	Week 24	Week 40	Week 24	Week 40	Week 24	Week 40
Q4W (n=115)	1858 (1719, 2007) [37]	2017 (1847, 2203) [41]	3.50 (3.2, 3.8) [39]	3.50 (3.3, 3.8) [37]	2.35 (2.2, 2.5) [32]	2.56 (2.4, 2.7) [32]	6.9 (0 – 29)	6.9 (0 – 28)
Q8W (n=115)	3037 (2786, 3310) [42]	3027 (2762, 3322) [47]	3.55 (3.2, 3.9) [56]	3.33 (3.1, 3.6) [47]	1.43 (1.3, 1.6) [54]	1.49 (1.4, 1.6) [42]	6.9 (0 – 59)	7.0 (0 – 57)
Oral)[f] (n=50)	------	------	------	------	4.51 (4.1, 5.0) [37]	4.54 (4.1, 5.0) [38]	------	------

a. Geometric mean (95% CI) [CVb%]

b. AUC(0-τ) = AUC(Week 24 to Week 28) for Q4W regimen (n=84), and AUC(Week 24 to Week 32) for Q8W regimen (n=86) or AUC(Week40 to Week 44) for Q4W (n=80) and AUC(Week40 to Week 48) for Q8W regimen (n=93)

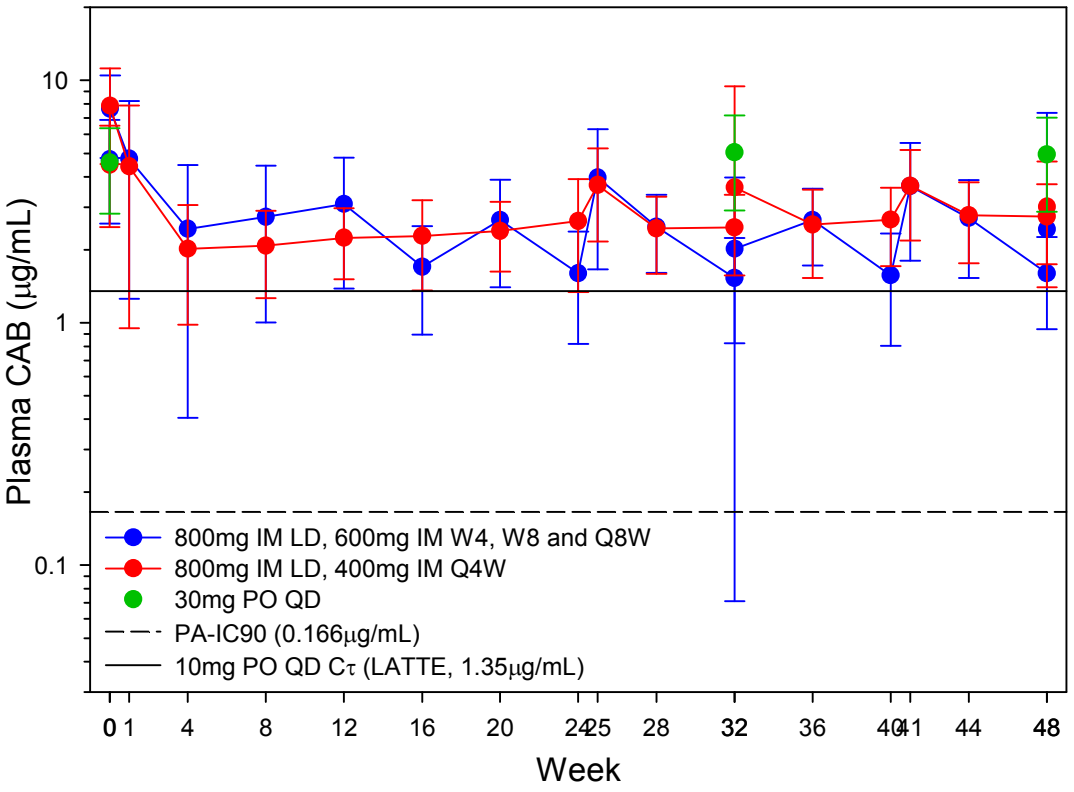
c. Cmax: Q4W: between Week 24 and Week 28 (n=97) or Week 40 and Week 44 (n=95); Q8W: between Week 24 to Week 32 (n=98) or Week 40 and Week 48 (n=104)

d. Individual Average C0 W24 observed using troughs at Week 20, Week 24, Week 28 and Week 32 for the Q4W arm (n=108) and at Week 24, and Week 32 for Q8W arm (n=100) and Individual Average C0 W40 using troughs at W40, 44, and 48 for Q4W (n=98) and W16, 24, 32, 40 and 48 for Q8W (n=112)

e. Tmax presented as median (range) in days, (Week 24-32: n=97 Q4W arm, n=98, Q8W arm; Week 40- 48: n=95 Q4W, n=104 Q8W)

f. Oral comparator arm combined troughs at Day 1, predose and at Week 32 ± Week 48.

Figure 2 **Mean (SD) Observed Concentration-Time Data following CAB LA Q8W and Q4W and Cτ (following 30mg Oral Once Daily[a]) through Week 48 (LATTE-2)**



a) Oral CAB 30 mg once daily administered for four weeks prior to first injection.

Table 4 Summary of Observed RPV PK Parameters following Repeat Dose Administration of Rilpivirine LA to HIV-infected Participants (LATTE-2)

Cohort	Plasma RPV PK Parameter[a]							
	AUC(0-τ)[b] (ng.h/mL)		Cmax[c] (ng/mL)		Individual Average C0[d] (ng/mL)		tmax[e] (d)	
	Week 24	Week 40	Week 24	Week 40	Week 24	Week 40	Week 24	Week 40
Q4W (n=115)	61309 (56724, 66264) [37]	71106 (65354, 77366) [39]	103 (94, 114) [49]	127 (118, 136) [36]	77.2 (72, 83) [35]	92.1 (87, 98) [32]	6.99 (0-29)	6 0. (0-28)
Q8W (n=115)	96196 (87286, 106015) [48]	116160 (108189, 124719) [35]	104 (95, 114) [47]	121 (111, 131)[42]	49.3 (46, 53) [41]	63.2 (59, 68) [35]	7.00 (0-57)	6 0. (0-59)

a. Geometric mean (95% CI) [Cvb%]

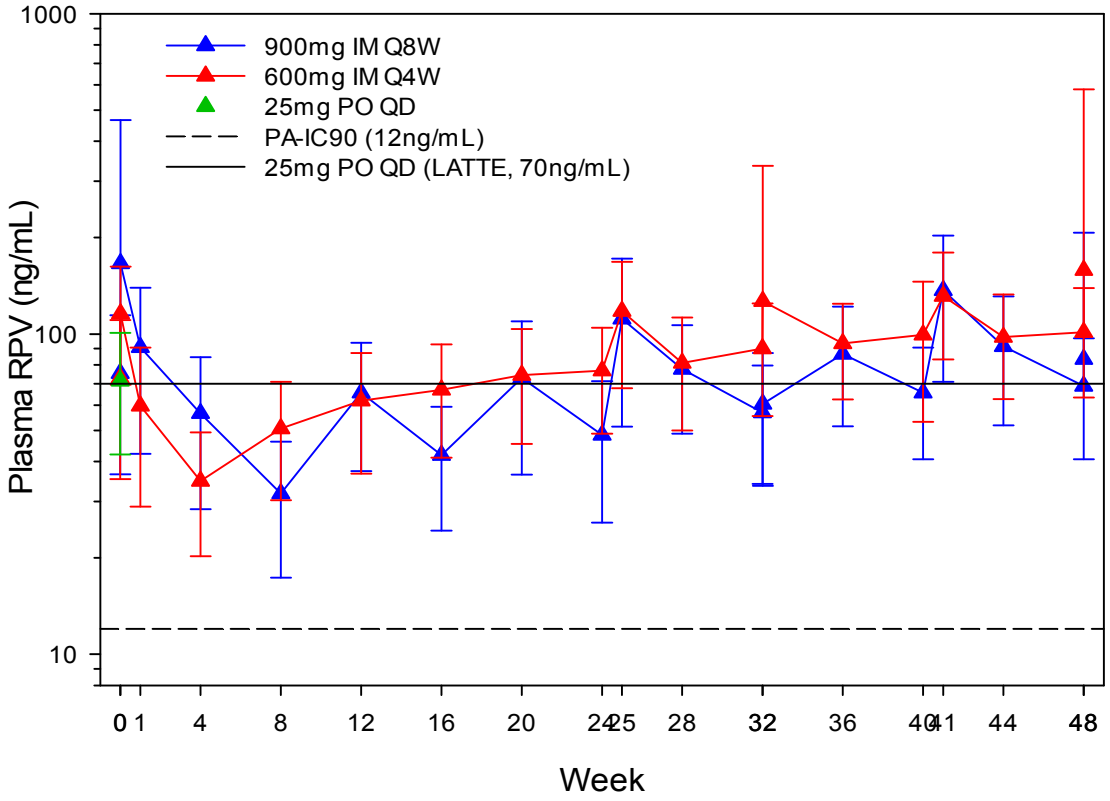
b. AUC(0-τ) = AUC(Week 24-Week 28) for Q4W regimen (n=84), and AUC(Week 24-Week 32) for Q8W regimen (n=86) or AUC(Week40 to Week 44) for Q4W (n=80) and AUC(Week40 to Week 48) for Q8W regimen (n=92) via non-compartmental PK analysis

c. Cmax: Q4W: between Week 24 and Week 28 (n=96) or Week 40 and Week 44 (n=94); Q8W: between Week 24 to Week 32 (n=97) or Week 40 and Week 48 (n=104)

d. Individual Average C0 W24 observed using troughs at Week 24, Week 28 and Week 32 for the Q4W arm (n=104) and at Week 24, and Week 32 for Q8W arm (n=101); Individual Average C0 W40 using troughs at W 36, 40, 44, and 48 for Q4W (n=102) and W40 and 48 for Q8W (n=100)

e. Tmax presented as median (range), (Week 24-32: :n=96 Q4W arm, n=97 Q8W arm; Week 40- 48: n=94 Q4W, n=104 Q8W)

Figure 3 Mean (SD) Observed Concentration-Time Data following RPV LA Q8W and Q4W through Week 48 and Day 1 Cτ (following RPV 25mg Oral Once Daily[a]) (LATTE-2)



a) Oral RPV 25 mg once daily administered for four weeks prior to first injection.

The Q4W dosing schedule for both CAB LA and RPV LA has been optimized for the present study. In LATTE-2, the Q4W dosing regimen for CAB LA included a 1st dose of 800 mg (two 2mL injections) at Day 1, followed by 400 mg IM Q4W starting at Week 4. For RPV LA in LATTE-2, the Q4W treatment arm was 600mg IM Q4W from Day 1. This specific schedule from the LATTE-2 Q4W dosing regimens for both compounds was modified for Phase 3 to align dosing for both compounds and minimize the number of injections needed. Both observed and model predicted CAB concentrations indicated that the loading dose strategy could be optimized while maintaining plasma concentrations during the early phase at levels associated with good efficacy and safety; i.e. by lowering the first CAB LA loading dose from 800 mg to 600 mg. This change reduces the number of injections to a single 3-mL injection for the first CAB LA injection (Week 4b in this protocol). For RPV LA, modeling and simulation indicates that a 900 mg IM loading dose (one 3 mL injection) on Day 1 rather than a 600mg IM first dose brings RPV plasma concentrations closer to steady-state values during the early phase. The dosing schedule in the protocol includes a 4 week oral lead-in beginning at Day 1. Therefore, the timing in the Time and Events Table translates to the following: Day 1, Week 4, and Q8W thereafter = Study Week 4b, and Q4W thereafter, respectively.

In summary, a modified Q4W dosing regimen that aligns the dosing of CAB LA + RPV LA to one injection of each compound at each visit was selected for Phase 3. The first injections of CAB LA and RPV LA will be administered as 3mL each, at doses of 600 mg and 900 mg, respectively. Subsequent injections of CAB LA and RPV LA will be 2mL each, at doses of 400 mg and 600 mg, respectively (see also Section 4.7.3).

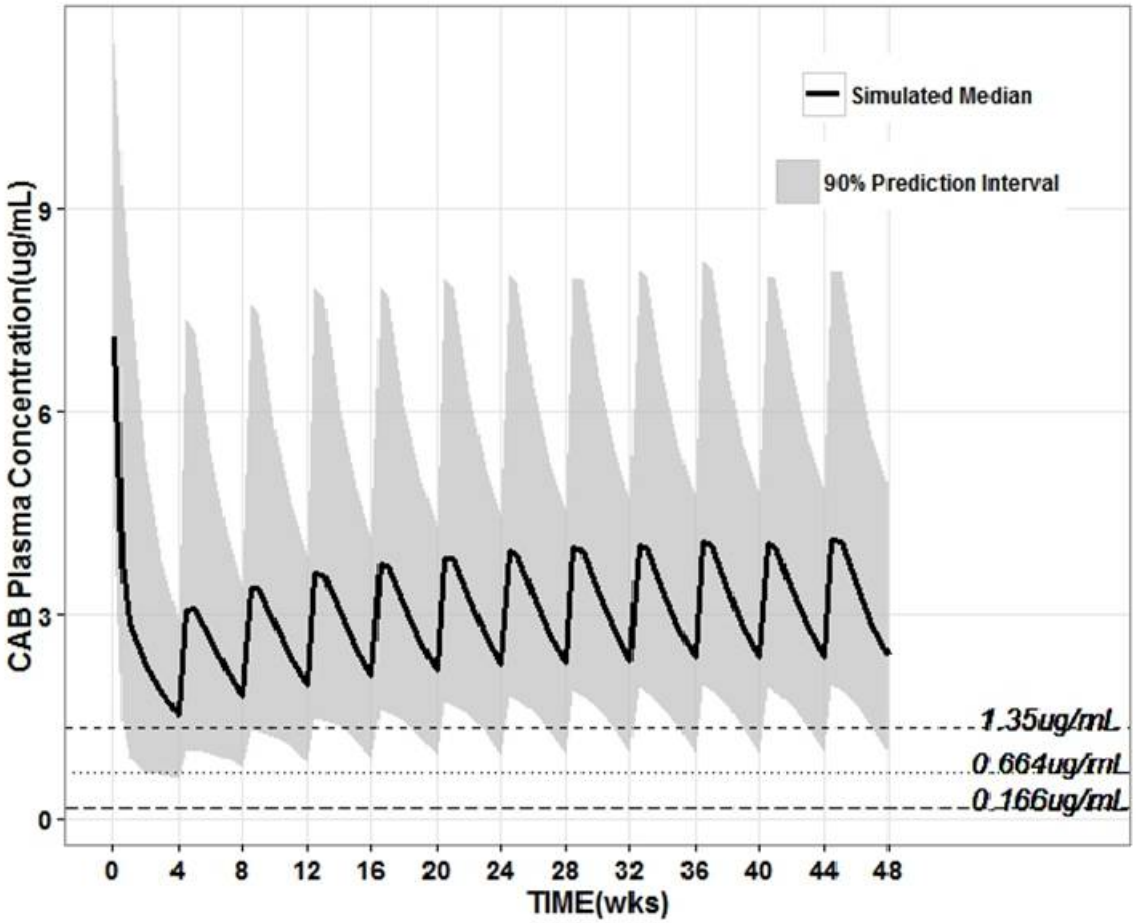
4.7.3. Modeling and Dose Simulations for CAB LA and RPV LA

Modeling and simulation was used to provide confidence in the selected regimen, inform the injection loading dose strategy, flexibility around dosing windows and the use of the oral bridging strategy.

4.7.3.1. CAB LA

For CAB LA, the model included data from 416 participants who received CAB LA IM as single or repeat administration, with approximately 50% of data obtained from 200056 (LATTE-2), ~20% from study 201120 (CAB LA pre-exposure prophylaxis [PrEP] study, GlaxoSmithKline Document Number 2015N229664_00) and ~30% from Phase 1 studies). The simulation of the predicted median (90% prediction interval [PI]) CAB concentration-time profile based on the population PK model is shown in Figure 4. The lower bound of the PI remains approximately at or above 4x-PA-IC90 throughout dosing. At steady state, 98% of the population is predicted to achieve trough concentrations above 4x the - Protein adjusted 90% inhibitory concentration (PA-IC90), and 88% are predicted to achieve trough concentrations above the geometric mean trough following the 10mg oral dose in LATTE of 1.35µg/mL (8-fold PA-IC90).

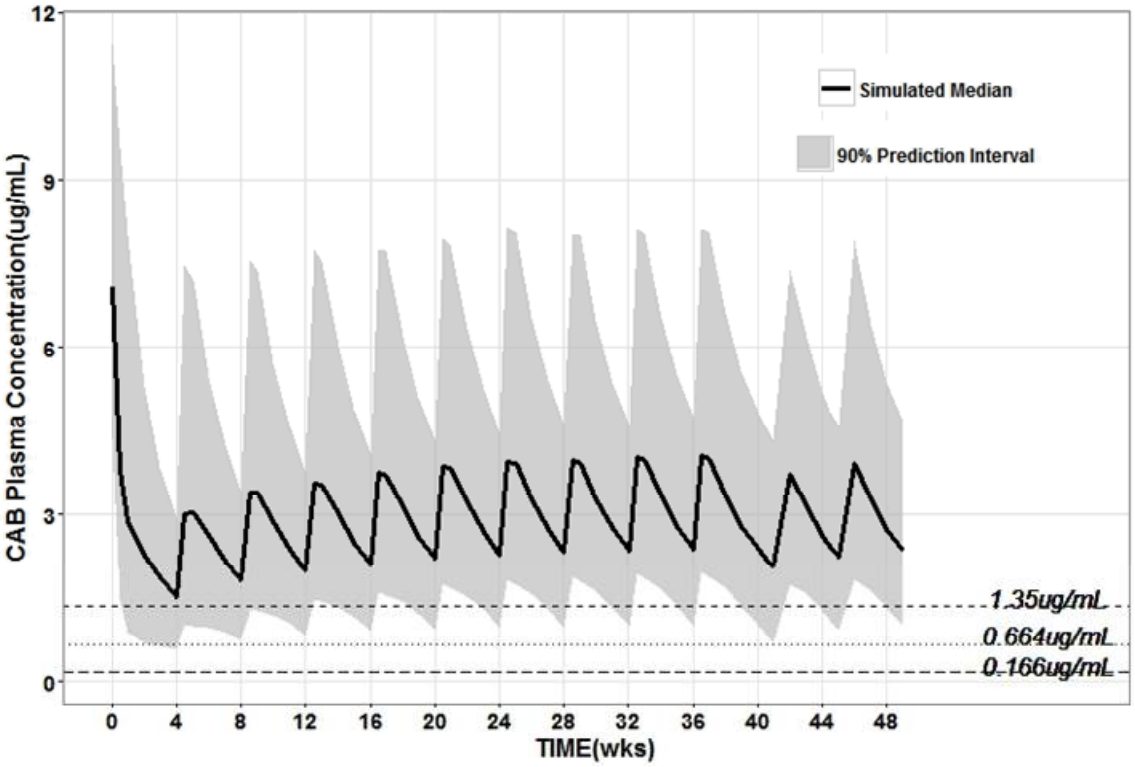
Figure 4 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the CAB LA Q4W Regimen (600 mg IM Day 1, then 400mg IM Q4W)^



Medium dashed line at 1.35µg/mL corresponds to the geometric mean Ctrough following oral CAB 10mg once daily (LATTE) and is equivalent to 8x PA-IC90
Dotted line at 0.664µg/mL corresponds to 4x PA-IC90
Long dashed line at 0.166 µg/mL corresponds to the PA-IC90.
*Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 4b study visit); Week 4 = second injections (Week 8 study visit)

At steady state, a one week delay in dosing of the Q4W regimen results in an approximately 15% reduction in median Cτ. With this delay, 95% are predicted to remain above 4x PA-IC90, and 79% are predicted to remain above the 10mg oral target (Figure 5). Simulations including delays greater than one week have been explored (not shown), with <70% of subjects remaining above the 10mg oral target. Therefore, a 1-week delay is the maximum allowed per the protocol.

Figure 5 Impact of a 1-week Delay in Dosing at Steady State (Week 40 delayed to Week 41) on Simulated* Median (90% PI) CAB Plasma Concentrations versus Time for the CAB LA Q4W regimen (600mg IM Day 1, then 400mg IM Q4W thereafter)^



Medium dashed line at 1.35µg/mL corresponds to the geometric mean Cτ following oral CAB 10mg once daily (LATTE) and is equivalent to 8x PA-IC90
Dotted line at 0.664µg/mL corresponds to 4x PA-IC90
Long dashed line at 0.166 µg/mL corresponds to the PA-IC90.
*Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = date of first injections (Week 4b study visit); Week 4 = second injections (Week 8 study visit)

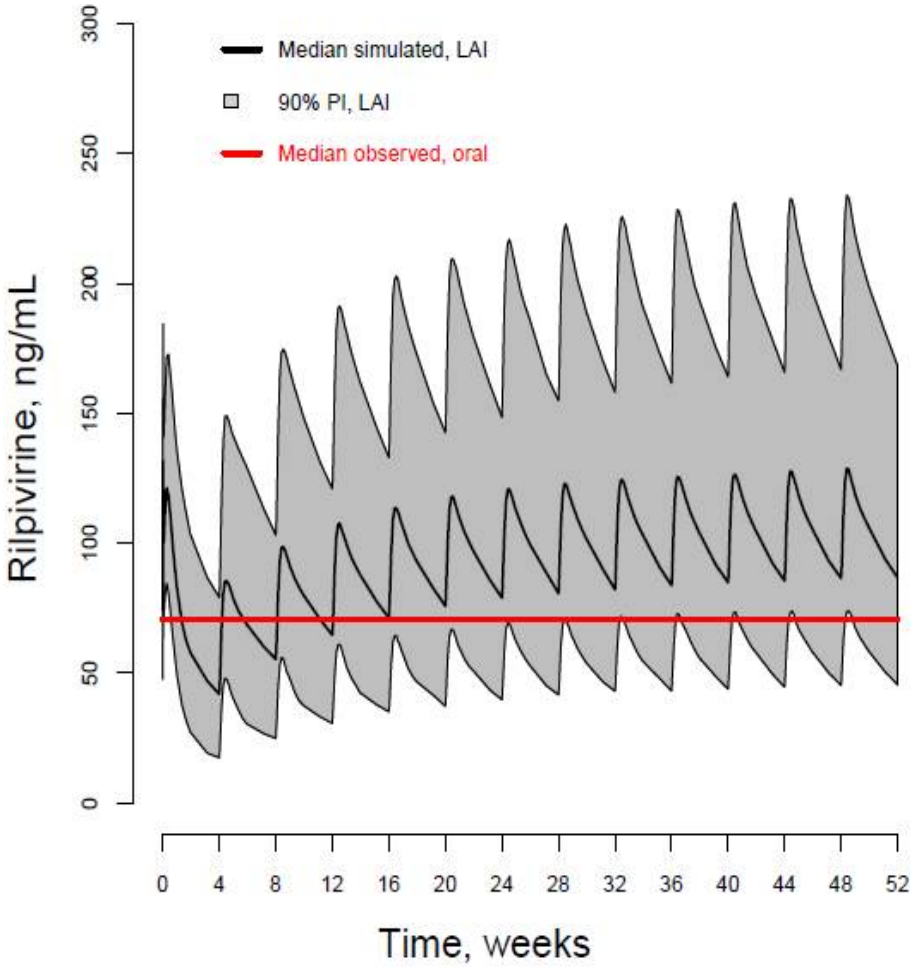
4.7.3.2. RPV LA

The Q4W regimen for this study was selected based on LATTE-2 safety and efficacy data as described above and supported by modeling and simulation of pharmacokinetic data obtained following administration of RPV LA in healthy participants (Phase 1 studies C158 and LAI115428 [GlaxoSmithKline Document Number 2011N112455_03]) and in HIV-infected participants (Phase 2 study LATTE-2), with the majority of the data coming from 200056 (LATTE-2).

The predicted median (90% PI) steady-state Cτ for the proposed regimen is 86.8 ng/mL (45.6 – 168 ng/mL; Figure 6). With this regimen, >99% of participants remain above the 5th percentile of steady state trough values following oral RPV 25mg (corresponding to 2x the PA-IC90). With a loading dose of 900 mg RPV LA on Day 1, the anticipated

median RPV Cτ at Week 4 is 42 ng/mL, with >98% of participants above the RPV PA-IC90.

Figure 6 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the RPV LA Q4W regimen (900 mg IM Day 1, then 600mg IM Q4Wa thereafter)^

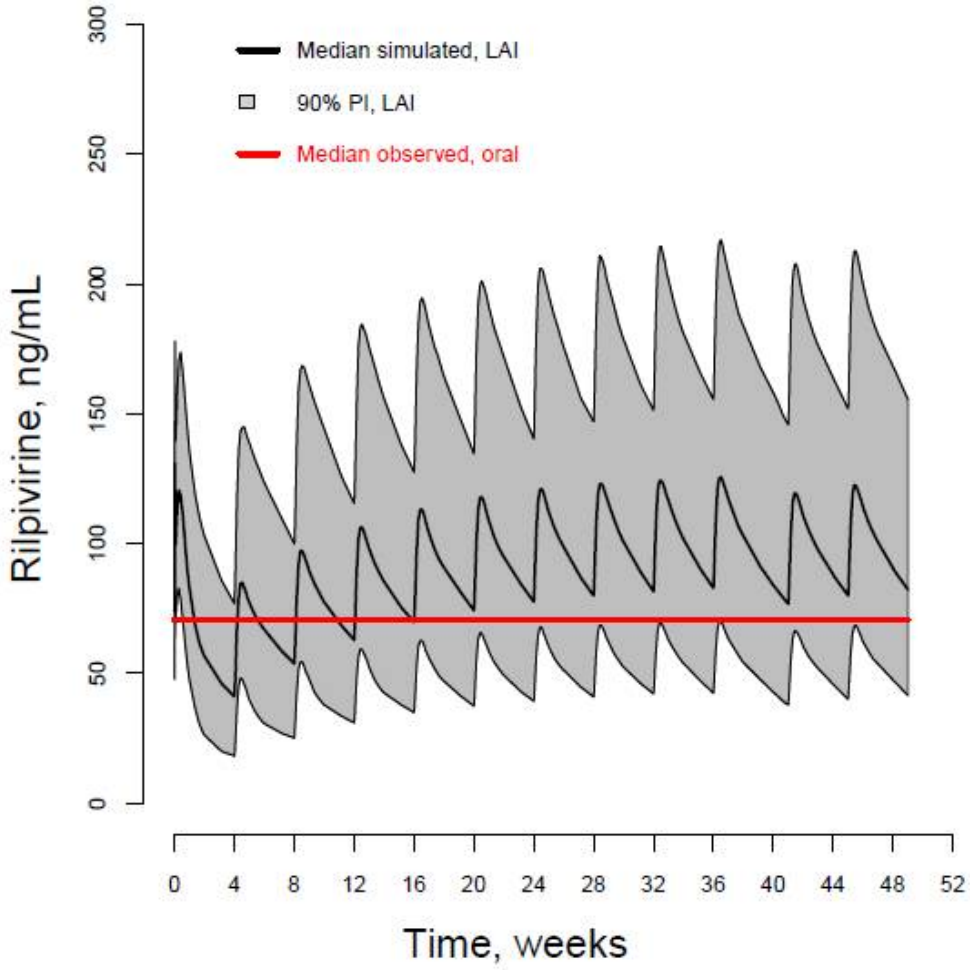


* Note: current simulations based on interim plasma concentration dataset. ^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 4b study visit); Week 4 = second injections (Week 8 study visit)

Horizontal line at 72 ng/mL corresponds to median Cτ following oral RPV 25mg once daily in LATTE-2 (oral lead-in) and is similar to median RPV Cτ in other studies in HIV-infected patients (LATTE, ECHO/THRIVE). Dotted lines correspond to 5th and 95th percentile of oral Cτ following oral RPV 25 mg once daily; 5th percentile (26.5 ng/mL) corresponds to 2x the PA-IC90 for RPV (2x 12 ng/mL)

At steady-state, a one week delay in dosing for the Q4W regimen is predicted to result in a median steady-state Cτ that remains above the median trough for RPV 25mg (Figure 7). This supports allowance of some flexibility in the dosing regimen.

Figure 7 Impact of 1-week Delay in Dosing at Steady State (Week 40 delayed to Week 41) on Simulated* Median (90% PI) RPV Plasma Concentrations versus Time for RPV LA Q4W dosing regimen (900 mg IM Day 1 and then 600 mg IM Q4W thereafter^)*



* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 4b study visit); Week 4 = second injections (Week 8 study visit)
Horizontal line at 72 ng/mL corresponds to median $C\tau$ following oral RPV 25mg once daily in LATTE-2 (oral lead-in) and is similar to median RPV $C\tau$ in other studies in HIV-infected patients (LATTE, ECHO/THRIVE)

4.8. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with oral and CAB LA or RPV LA can be found in the Investigator's Brochures (GlaxoSmithKline Document Number RH2009/00003/06, 2015; RPV IB, 2017).

Oral RPV is an approved medicinal product and detailed information on its benefit/risk profile together with any risk mitigation measures are described in product labeling (Edurant®, 2015). Current ART administered in this protocol have 2 NRTIs plus INI, NNRTI or PI as the third agent. Current ART are established antiretroviral treatments that have been in clinical use for several years and have well established benefit/risk profiles described in detail in their respective product labels.

The following section outlines the risk assessment and mitigation strategy for this protocol:

4.8.1. Risk Assessment

Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)

Since CAB is at an early stage of clinical development, and exposure in humans with or without HIV infection is limited, the clinical safety profile in humans has yet to be fully elucidated. The following risks have primarily been identified during routine preclinical testing and/or in the clinical trial experience to date and are considered of potential relevance to clinical usage in the context of this protocol. Additional information about the clinical experience to date and possible risks associated with treatment using CAB can be found in the Summary of Data and Guidance for the Investigator section of the IB.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Drug Induced Liver Injury (DILIs)	A small proportion of participants in the CAB program to date (total exposure approximately 1198 to 01 April 2016) have developed transaminitis (elevated liver transaminases characterised by predominant Alanine aminotransferase (ALT) elevation). In some of these participants' transient transaminitis were explained by acute hepatitis C infection whilst a small number of others did not have alternative explanations, suggesting a mild form of Drug induced liver injury (DILI) without hepatic dysfunction which resolved upon withdrawal of treatment with CAB. Of the five participants with possible or probable cases of DILI identified in Phase 2 studies, four participants were receiving oral CAB and one participant developed probable DILI following CAB IM or Placebo IM administration.	• Exclusion criteria as described in Section 5.2 will prohibit participants with significant liver impairment based on screening liver chemistry including transaminases (ALT and Aspartate aminotransferase [AST]) as well on prior medical history. Participants with a history of chronic liver disease with ongoing inflammation and/or fibrosis will have additional confirmatory assessments to confirm suitability for entry into the study. • A 4-week oral lead- in Phase is being implemented in this study, where all participants will receive oral CAB prior to the administration of IM CAB to determine individual safety and tolerability • Liver transaminases (ALT and AST) will be closely monitored throughout this study (refer to Time & Events Table) and the liver chemistry stopping criteria will be adopted as described in Section 5.5.1.1 of this protocol. Participants will be withdrawn from CAB treatment where no compelling alternative cause is identified and DILI is suspected. • Participants who develop ALT ≥3 times the upper limit of normal (ULN) while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA + RPV LA.
Injection Site Reactions (ISRs)	Clinical, experience to date has demonstrated ISRs occur in the majority of exposed participants treated with CAB LA but are generally mild (Grade 1) or moderate (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days duration (median duration for individual events <1 week). ISRs may occur more than once in an individual participant	• Administration advice will be given to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and treatment of ISRs is given in study documentation • Advice will be given to participants on care of injection site on day/days immediately post

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well tolerated and have not to date been associated with an excess of participants' withdrawal. None of the ISRs reported to date was serious and no clinically significant complications were reported	administration, use of analgesia, compresses where appropriate. • Participants will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. • Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored • Significant ISRs may be photographed and referred to a dermatologist for specialist advice.
Hypersensitivity Reactions (HSR)	Hypersensitivity reactions have been reported as uncommon occurrences with integrase inhibitors, including the closely related compound dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. While there have been no clinical cases of hypersensitivity to CAB, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic symptoms associated with use of IM CAB. The long exposures anticipated after IM CAB injection may complicate the management of a drug hypersensitivity reaction, were it to occur.	• The risk of developing a hypersensitivity reaction post administration of IM CAB will be minimized by the use of a 4-week oral lead-in of oral CAB to determine individual safety and tolerability prior to the introduction of IM CAB. • Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study (refer to Time & Events Table, Section 7.1). Results from these assessments may aid early detection of HSR. • Oral CAB will be withdrawn immediately for cases with suspected HSR during the oral CAB lead-in phase and would not proceed to the injection phase. Participants in the injection phase would not receive further injections. During oral and IM CAB treatment, any HSR reactions that occur would be managed supportively.
Development of Resistance following	Residual concentrations of CAB would remain in the systemic	• Alternative oral HAART regimens will be prescribed within

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
discontinuation of CAB LA	circulation of participants who stopped CAB LA treatment for prolonged periods (more than 1 year, in some subjects, GlaxoSmithKline Document Number 2016N269422_00) despite stopping treatment (e.g., for tolerability issues or treatment failure). Participants discontinuing CAB LA regimen may be at risk for developing HIV-1 resistance to CAB many weeks after discontinuing injectable therapy.	4 weeks after participants stop CAB LA. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimizing the risk of emergent resistance • The participants in this study who discontinue IM CAB for any reason will be monitored for a minimum of 52 weeks from the time of the last IM CAB injection.
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for CAB and CAB LA, refer to Section 6.13 CAB and CAB LA should not be co-administered with the following medicinal products, as significant decreases in CAB plasma concentrations may occur (due to UGT enzyme induction), which may result in loss of therapeutic effect of CAB. - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin - the antimycobacterials rifampicin, rifapentine, rifabutin - St John's wort (Hypericum perforatum). Chronic use of oral glucocorticoids must be avoided; however, short treatment courses (for example, 21 days or less) and topical, inhaled or intranasal use of glucocorticoids will be allowed. Oral CAB administration only: Antacid products containing divalent cations (e.g., aluminium, calcium and magnesium) must be taken at least 2 hours before or at	• All participants will be informed of prohibited medications throughout the study and updates provided as needed via the informed consent.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	least 4 hours after CAB Participants discontinuing a LA regimen may be at risk for developing DDIs many weeks after discontinuing injectable therapy.	
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that CAB LA can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of CAB. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of overdose with CAB LA are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration. CAB	• Training will be provided to all sites on proper injection technique. • Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose electrocardiogram (ECG) , vital signs, or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor will be notified. • Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all participants. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints for determination of CAB concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB concentrations.
ORAL RPV For safety and risk mitigation for oral RPV refer to the RPV local prescribing information [Edurant ® Product Information, 2015]. **RPV LA** Information about the clinical experience to date and possible risks associated with treatment using RPV LA can be found in the Summary of Data and Guidance for the Investigator section of the IB. Beyond what has already been identified with oral RPV, no new systemic adverse reactions to RPV LA (same active moiety) have been observed. The following risks are considered to be of specific clinical relevance in the context of IM use		

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Injection Site Reactions	Clinical, experience to date has demonstrated ISRs occur in the majority of exposed participants treated with RPV LA but are generally mild (Grade 1) or moderate (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days duration (median duration for individual events <1 week). ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well tolerated and have not to date been associated with an excess of participants' withdrawal due to ISRs. None of the ISRs was serious and no clinical significant complications were reported	• Administration advice to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and treatment of ISRs given in study documentation • Advice to participants on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate. • Participants will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. • Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored • Significant ISRs may be photographed and referred to a dermatologist for specialist advice.
Rash	Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are Grade 1 or 2). Severe skin and hypersensitivity reactions have been reported during the postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with oral RPV containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries.	• In this study, RPV LA administration will be preceded by an oral RPV lead in to evaluate safety and tolerability in individual participants. • Participants with a grade 1 or 2 rash will be allowed to continue treatment or to be rechallenged, depending on the clinical judgment of the investigator. • All participants experiencing a grade 3 or 4 rash should discontinue their ARV medication (study medication and background regimen) and be withdrawn from the study. • All rash events should be assessed

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
		with special attention to systemic symptoms, laboratory abnormalities, or mucosal involvement. Close clinical follow-up, including follow-up of laboratory abnormalities, and appropriate medical intervention, including referral to dermatologist as appropriate, should be instituted for these events; daily follow-up is recommended for 5 days from the onset of the event to monitor for progression of the event. See Section 7.4.4.13 for additional guidance on management of rash events.
Development of Resistance	Residual concentrations of RPV LA can remain in the systemic circulation of participants who stopped treatment (e.g., for tolerability issues or treatment failure) for prolonged periods (months to more than a year, in some subjects, McGowan, 2016). Participants discontinuing a LA regimen may be at risk for developing resistance to RPV many weeks after discontinuing injectable therapy.	• Alternative oral HAART regimens will be prescribed within 4 weeks after participants stop RPV LA. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimizing the risk of emergent resistance • The Sponsor will continue to monitor participants in this study who discontinue a LA regimen for any reason for a minimum of 52 weeks from the time of the last LA administration.
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for RPV and RPV LA, refer to Section 6.13 RPV LA should not be co-administered with the following medicinal products, as significant decreases in RPV plasma concentrations may occur (due to CYP3A enzyme induction), which may result in loss of therapeutic effect of RPV LA. - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin - the antimycobacterials	• All participants will be informed of prohibited medications throughout the study and updates provided as needed via informed consent.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	rifampicin, rifapentine, rifabutin - the glucocorticoid systemic dexamethasone, except as a single dose treatment - St John's wort (Hypericum perforatum). Of note, evidence to date indicates that clinically relevant DDIs with RPV LA and other antiretrovirals are unlikely to occur. Oral RPV administration only: - Antacid products containing divalent cations (e.g., aluminium, calcium and magnesium) must be taken at least 2 hours before or at least 4 hours after RPV. - H2-antagonists must be taken at least 12 hours before or at least 4 hours after taking RPV. - RPV should not be co-administered with proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole;	

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that RPV LA can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of RPV. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. Accidental intravenous administration may result in overdose shortly after injection. In general, no cases of overdosage with RPV have been described to date. In addition, HIV-1 viral suppression may not be effective following accidental maladministration.	• Training will be provided to all sites on proper injection technique. • Should IM maladministration be suspected at any time (e.g., suspected under or overdose or inadvertent IV dosing), post dose ECG monitoring and vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified • Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all participants. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints for determination of RPVconcentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB and RPV concentrations.
Study Procedures		
Risks of ECG pad removal	Participants will be required to have ECG tracings recorded periodically throughout the study	• Some discomfort and rash may occur where the ECG pads are removed.
Other		
Risk of Treatment Failure	This study employs a novel maintenance approach to the treatment of HIV-1 infection. Following viral suppression, participants will be transitioned off of a 3 drug ART regimen to a 2 drug LA ART regimen that remains experimental. Although both IM CAB and RPV have demonstrated antiviral activity in large clinical studies and the two drug combination has demonstrated antiviral activity in study	Viral loads will be closely monitored throughout the study. Plasma samples will be collected throughout the Maintenance Phase for determination of CAB and RPV concentration and possible pharmacokinetic correlation with virologic response. HIV-1 RNA viral loads will be closely

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	LAI116482, the risk of virologic failure in study 200056 is unknown. Doses of the CAB LA and RPV LA have been selected to achieve exposures that are expected to maintain virologic efficacy on the basis of available data with the oral formulations. Due to administration error, it is possible that a participant could receive an inadequate dose of CAB LA or RPV LA. Sub-therapeutic concentrations of either CAB LA or RPV LA could lead to virologic failure and possibly the development of resistance.	monitored throughout the injection period of the study.

4.8.1.1. Other Clinically Relevant Information

Additional details concerning safety observations from clinical studies and for which a causal association has not been established or which are of minimal clinical significance may be found in the Investigator's Brochures (GSK Document number RH2009/00003/06 [CAB IB], RPV IB, 2017).

Adverse Events of Special Interest:

Seizure
Three cases of seizures have occurred in the cabotegravir programme cumulatively through 15 May 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. Overall, there is not convincing evidence that cabotegravir 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. However seizure and seizure-like events are considered as AEs of special interest for close monitoring in future studies. Subjects with recent history of, or recent treatment for, seizure will be excluded from study participation.

4.8.2. Benefit Assessment

The antiviral activity against HIV-1 of CAB has been well established through Phase 2a and Phase 2b studies. RPV is an established antiviral agent against HIV-1 in treatment naive patients, with long term durability (>96 weeks in Phase 3 and >240 weeks in Phase IIb).

Participants receiving CAB LA + RPV LA are anticipated to benefit from maintenance of virological suppression using LA agents. Participants randomized to an arm containing CAB LA+ RPV LA will have Q4 weekly dosing without the need to take concomitant daily oral therapy. Adherence in these participants is expected to be improved and will be directly observed during IM injections. Efficacy of the two-drug regimen, as oral agents, has been demonstrated through Week 96 of the ongoing LAI116482 study. Efficacy of the two-drug regimen, as IM agents, has been demonstrated through Week 48 of the ongoing 200056 study. The reduction in ART, and the discontinuation of NRTIs, may offer long term safety and tolerability benefits in these participants.

4.8.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating 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.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational regimen or other study treatment that may impact participant eligibility is provided in the current Investigator's Brochures (IB) for CAB (GlaxoSmithKline Document Number RH2009/00003/06, 2016) and RPV(RPV IB, 2017) and RPV product label.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A participant will be eligible for inclusion in this study only if all of the following criteria apply:

- Be able to understand and comply with protocol requirements, instructions, and restrictions;
- Understand the long term commitment to the study and be likely to complete the study as planned;

- Be considered appropriate candidates for participation in an investigative clinical trial with oral and intramuscularly injectable medications (e.g., no active substance use disorder, acute major organ disease, or planned long-term work assignments out of the country, etc.).

The following are study specific eligibility criteria unless stated otherwise. **In addition to these criteria, Investigators must exercise clinical discretion regarding selection of appropriate study participants, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP). All participants must be considered appropriate candidates for antiretroviral therapy in accordance with local treatment guidelines**.

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility. In exceptional circumstances only, if a repeat lab is required because a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor for consideration of participant eligibility. A repeat central lab will be submitted concurrently or at the next planned visit.

Source documentation to verify entry criteria must be reviewed by the Principal Investigator or designee prior to randomization. Source documents from other medical facilities must be located/received during the 14 day screening phase (or up to 35 days) and under no circumstances may the participant be randomized in the absence of source documentation.

Participants eligible for enrolment in the study must meet all of the following criteria:

AGE
1. Aged 18 years or older (or ≥19 where required by local regulatory agencies), at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Must be on uninterrupted current regimen (either the initial or second ARV regimen) for at least 6 months prior to Screening. Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done for treatment failure (HIV-1 RNA ≥400 c/mL). Acceptable stable (initial or second) ARV regimens prior to Screening include 2 NRTIs plus: • INI with the exception of ABC/DTG/3TC (either the initial or second cART regimen) • NNRTI (either the initial or second cART regimen) • Boosted PI (or atazanavir [ATV] unboosted) (must be either the initial cART regimen or one historical within class switch is permitted due to safety/tolerability) The addition, removal, or switch of a drug(s) that has been used to treat HIV

based on antiretroviral properties of the drug constitutes a change in ART with the following limited exceptions:

- Historical changes in formulations of ART drugs or booster drugs will not constitute a change in ART regimen if the data support similar exposures and efficacy, and the change must have been at least 3 months prior to Screening.
- Historical perinatal use of an NRTI when given in addition to an ongoing HAART will not be considered a change in ART regimen.
- A change in dosing scheme of the same drug from twice daily to once daily will not be considered a change in ART regimen if data support similar exposures and efficacy.

3. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening;

4. Plasma HIV-1 RNA <50 c/mL at Screening;

SEX

5. A female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test at screen and a negative urine hCG test at Randomization), not lactating, and at least one of the following conditions applies:
   a. ***Non-reproductive*** potential defined as:
   - Pre-menopausal females with one of the following:
     - Documented tubal ligation
     - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
     - Hysterectomy
     - Documented Bilateral Oophorectomy
   - Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to

study enrolment. b. **Reproductive potential** and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 12.7.1, Appendix 7) from 30 days prior to the first dose of study medication, and until from 30 days prior to the first dose of study medication throughout the study, and for at least 30 days after discontinuation of all oral study medications and for at least 52 weeks after discontinuation of CAB LA and RPV LA. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.
INFORMED CONSENT
Capable of giving signed informed consent as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Eligible participants or their legal guardians (and next of kin when locally required), must sign a written Informed Consent Form before any protocol-specified assessments are conducted. Enrolment of participants who are unable to provide direct informed consent is optional and will be based on local legal/regulatory requirements and site feasibility to conduct protocol procedures.
OTHER
Participants enrolled in France must be affiliated to, or a beneficiary of, a social security category.

All participants participating in the study should be counselled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to an uninfected partner.

5.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential. A participant will not be eligible for inclusion in this study if any of the following criteria apply:

Exclusionary Criteria prior to Screening or Day 1
1. Within 6 months prior to Screening and after confirmed suppression to <50 c/mL on current ART regimen, any plasma HIV-1 RNA measurement ≥50 c/mL 2. Within the 6 to 12 month window prior to Screening and after confirmed suppression to <50 c/mL, any plasma HIV-1 RNA measurement >200 c/mL, or 2 or more plasma HIV-1 RNA measurements ≥50 c/mL 3. Any drug holiday during the window between initiating first HIV ART and 6

months prior to Screening, except for brief periods (less than 1 month) where all ART was stopped due to tolerability and/or safety concerns 4. Any switch to a second line regimen, defined as change of a single drug or multiple drugs simultaneously, due to virologic failure to therapy (defined as a confirmed plasma HIV-1 RNA measurement ≥400 c/mL after initial suppression to <50 c/mL while on first line HIV therapy regimen) 5. Abacavir/dolutegravir/lamivudine, (ABC/DTG/3TC) as current ART regimen 6. A history of use of any regimen consisting of only single NNRTI therapy (even if only for peri-partum treatment), or only single or dual NRTI therapy prior to starting cART 7. Participants who are currently participating in or anticipate to be selected for any other interventional study
Exclusionary medical conditions
8. Women who are pregnant, breastfeeding or plan to become pregnant or breastfeed during the study 9. Any evidence of an active Center for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy and historical or current CD4 cell counts less than 200 cells/mm3 10. Participants with moderate to severe hepatic impairment 11. Any pre-existing physical or mental condition (including substance use disorder) which, in the opinion of the Investigator, may interfere with the participant's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participant 12. Participants determined by the Investigator to have a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder. A participant with a prior history of seizure may be considered for enrolment if the Investigator believes the risk of seizure recurrence is low. All cases of prior seizure history should be discussed with the Medical Monitor prior to enrolment 13. All participants will be screened for syphilis (rapid plasma reagin [RPR]). Participants with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded. Participants with a serofast RPR result (persistence of a reactive nontreponemal syphilis test) despite history of adequate therapy and no evidence of re-exposure may enrol after consultation with the Medical Monitor. Participants with a positive RPR test who have not been treated may be rescreened at least 30 days after completion of antibiotic treatment for syphilis 14. Participants who, in the investigator's judgment, pose a significant suicide risk. Participant's recent history of suicidal behavior and/or suicidal ideation should be considered when evaluating for suicide risk 15. The participant has a tattoo or other dermatological condition overlying the

gluteus region which may interfere with interpretation of injection site reactions

16. Evidence of Hepatitis B virus (HBV) infection based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs) and HBV DNA as follows:

    •Participants positive for HBsAg are excluded;

    •Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded

Note: Participants positive for anti-HBc (negative HBsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded.

17. Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; participants who are anticipated to require HCV treatment within 12 months must be excluded. (HCV treatment on study may be permitted post Week 48, following consultation with the medical monitor)

Participants with HCV co-infection will be allowed entry into phase 3 studies if:

- Liver enzymes meet entry criteria
- HCV Disease has undergone appropriate work-up, and is not advanced, and will not require treatment prior to the Week 48 visit. Additional information (where available) on participants with HCV co-infection at screening should include results from any liver biopsy, Fibroscan, ultrasound, or other fibrosis evaluation, history of cirrhosis or other decompensated liver disease, prior treatment, and timing/plan for HCV treatment.
- In the event that recent biopsy or imaging data is not available or inconclusive, the Fib-4 score will be used to verify eligibility
    - Fib-4 score > 3.25 is exclusionary
    - Fib-4 scores 1.45 – 3.25 requires Medical Monitor consultation

Fibrosis 4 Score Formula:

(Age x AST) / (Platelets x (sqr [ALT])

18. Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice or cirrhosis), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment)
19. History of liver cirrhosis with or without hepatitis viral co-infection.
20. Ongoing or clinically relevant pancreatitis
21. Clinically significant cardiovascular disease, as defined by history/evidence of congestive heart failure, symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or any clinically significant cardiac disease
22. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell

carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the Study medical monitor for inclusion of the participant prior to randomization 23. Any condition which, in the opinion of the Investigator, may interfere with the absorption, distribution, metabolism or excretion of the study drugs or render the participant unable to receive study medication 24. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class. In addition, if heparin is used during PK sampling, participants with a history of sensitivity to heparin or heparin-induced thrombocytopenia must not be enrolled 25. Current or anticipated need for chronic anti-coagulation with the exception of the use of low dose acetylsalicylic acid (≤325mg)
Exclusionary Laboratory Values or Clinical Assessments at Screening (a single repeat to determine eligibility is allowed)
26. Any evidence of primary resistance based on the presence of any major known INI or NNRTI resistance-associated mutation, except for K103N, (International AIDS Society [IAS]-USA, 2015) by any historical resistance test result. Note: Prior genotypic resistance testing is not required but if available it must be provided to GSK, after screening and before randomization according to guidance in the SPM, to provide direct evidence of no pre-existing exclusionary resistance mutations. You must wait for the study virologists to confirm the lack of exclusionary resistance mutations, which will be provided before the screening window closes. Details regarding baseline or prior resistance data must be noted in the source documentation 27. Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening phase to verify a result 28. Any acute laboratory abnormality at Screening, which, in the opinion of the investigator, would preclude the participant's participation in the study of an investigational compound 29. Participant has estimated creatine clearance <50mL/min per 1.73m^2 via CKD-EPI Method 30. Alanine aminotransferase (ALT) ≥3 × ULN
Concomitant Medications
31. Exposure to an experimental drug or experimental vaccine within either 30 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to Day 1 of this study; 32. Treatment with any of the following agents within 28 days of Screening: • radiation therapy; • cytotoxic chemotherapeutic agents;

- tuberculosis therapy with the exception of isoniazid (isonicotinylhydrazid, INH);
- anti-coagulation agents;
- Immunomodulators that alter immune responses such as chronic systemic corticosteroids, interleukins, or interferons. Note: Participants using short-term (e.g. ≤21 days) systemic corticosteroid treatment; topical, inhaled and intranasal corticosteroids are eligible for enrolment.

33. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening
34. Treatment with any agent, except recognized ART as allowed above, with documented activity against HIV-1 within 28 days of study Day 1
35. Use of medications which are associated with Torsade de Pointes. (See SPM for a list of relevant medications)
36. Current or prior history of etravirine (ETR) use
37. Current use of tipranavir/ritonavir or fosamprenavir/ritonavir
38. Participants receiving any prohibited medication listed in Section 6.13.2 and who are unwilling or unable to switch to an alternate medication. Note: Any prohibited medications listed in Section 6.13.2 that decrease CAB or RPV concentrations should be discontinued for a minimum of four weeks or a minimum of three half-lives (whichever is longer) prior to the first dose and any other prohibited medications should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose (see Section 6.13.2 for details of prohibited medications)

5.3. Additional Eligibility Criteria

To assess any potential impact on participant eligibility with regard to safety, the investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the study drugs.

Notwithstanding these minimum inclusion and exclusion criteria, investigators must also follow country specific guidelines where they exist when making decisions about participants who are eligible for study participation.

5.4. Screening/Baseline/Run-in Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.3.2).

A single repeat of a procedure / lab parameter is allowed to determine eligibility (unless otherwise specified).

Participants are allowed to re-screen for this study one time. This will require a new participant number.

5.5. Withdrawal/Stopping Criteria

Participants permanently discontinuing study treatments prior to the Week 52 visit are considered to be withdrawn from the study treatments. Participants who enter the Extension Phase but permanently discontinue participation in the Extension Phase prior to commercially available CAB LA + RPV LA are considered to be withdrawn from the study treatments but are not considered to be withdrawn from the study because they will enter the follow Follow-up Phase.

A participant may withdraw consent and discontinue participation in this study at any time at his/her own request. The investigator may also, at his or her discretion, discontinue the participant from participating in this study at any time (e.g., safety, behavioural or administrative reasons). If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. Withdrawn participants will not be replaced.

All participants who discontinue prematurely from the study, irrespective of arm, will be asked for additional information to establish the reason for withdrawal.

Participants are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the Investigator on the Completion/Withdrawal section of the electronic case report form (eCRF). Every effort should be made by the Investigator to follow-up participants who withdraw from the study.

Participants may have a temporary interruption to their study treatment for management of toxicities.

Participants <u>may</u> be prematurely discontinued from the study for any of the following reasons:

- Adverse event / Serious adverse event
- Protocol deviation
- Intolerability of injections
- Participant lost to follow-up
- Participant or Investigator non-compliance;
- Termination of the study by the Sponsor
- At the request of the participant, Investigator, GSK or ViiV Healthcare;

- The participant requires concurrent prohibited medications during the course of the study. The participant may remain in the study if in the opinion of the Investigator and the medical monitor; such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the participant.

Participants must be discontinued from the study for any of the following reasons:

- Participants who are not eligible to continue into the Maintenance Phase.
- Participants who are not eligible, or do not wish to continue on to the Extension Phase.
- Virologic withdrawal criteria as specified in Section 5.5.4 are met;
- For participants in the current ART arm during the Maintenance Phase, plasma HIV-1 RNA ≥50 c/mL at Week 48 with a confirmatory retest;
- Participant requires substitution or dose modification of current ART;
- Participant requires substitution or dose reduction of CAB LA or RPV LA (oral bridging supply and potential for a second loading dose may be permissable following discussion with the Medical Monitor).
- Liver toxicity where stopping criteria are met and no compelling alternate cause is identified (see Section 5.5.1);
- Renal toxicity are met and no compelling alternate cause is identified;
- QT interval (QTc) interval > 550 msec from three or more tracings separated by at least 5 minutes and considered causally related to IP.
- Grade 4 clinical AE considered causally related to study drug;
- Participant has a Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement and no compelling alternative cause is identified
- Pregnancy (intrauterine), regardless of termination status of pregnancy.
- Participant withdrew consent

Efficacy data for participants withdrawing from the study will be considered evaluable up to the point at which they are withdrawn using the same criteria for evaluability as for participants who complete the study.

Safety data for all participants who receive any amount of study drug, including participants who withdraw from the study, will be included in evaluations of safety.

If a participant is prematurely or permanently withdrawn from the study, the procedures described in the Time and Events Table for the in-clinic Withdrawal visit are to be performed. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study medication for participants with ongoing AEs, and serious adverse events (SAEs)

related & not related to study drug and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit.

All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any participant from the study.

The following actions must be taken in relation to a participant who fails to attend the clinic for a required study visit:

- The site must attempt to contact the participant and re-schedule the missed visit as soon as possible.
- The site must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- In cases where the participant is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and if necessary a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A participant may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.5.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

IP will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin, bilirubin fractionation required).

  NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, sites should evaluate **the presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a participant meets the criterion of total bilirubin ≥ 2xULN, then the event meets liver stopping criteria.

- ALT ≥8xULN.

- ALT ≥3xULN (if Baseline ALT is < ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR;
- ALT ≥3x Baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5xULN and <8xULN that persists ≥2 weeks (with bilirubin <2 ULN & no signs or symptoms of acute hepatitis or hypersensitivity).
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks.

See Section 5.5.1.1 for Participant Management and Follow-Up.

5.5.1.1. Liver Chemistry Stopping Criteria, Participant Management and Follow-Up

Participants who develop ALT ≥5xULN must be followed weekly until resolution or stabilization (ALT <5xULN on 2 consecutive evaluations).

When any of the liver chemistry stopping criteria is met, do the following:

- Immediately hold IP. If on LA therapy, **do not** administer another injection until approval is received from the ViiV Safety and Labelling Committee.
- Report the event to the Medical Monitor within 24 hours of learning its occurrence (Section 7.4.3.4).
- Complete the liver event eCRF and SAE eCRF, where applicable, (see Section 7.4.3.4)
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
- Perform liver event follow up assessments (described below), and monitor the participant until liver chemistries resolve, stabilize, or return to Baseline values as described below.
- Make every reasonable attempt to have participants return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor participants twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within Baseline values.

Make every attempt to carry out the **liver event follow up assessments** described below:

Viral hepatitis serology including:

- Hepatitis A immunoglobulin M (IgM) antibody;
- Hepatitis B surface antigen (HBsAg) and Hepatitis B Core Antibody (IgM);

  - Hepatitis C RNA;
  - Hepatitis E IgM antibody;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Serum acetaminophen test (APAP adduct test). The site must contact GSK when this test is required. Please refer to the central laboratory manual.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Fractionated bilirubin, if total bilirubin is greater than 1.5xULN;
- Obtain complete blood count with differential to assess eosinophilia;
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins);
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form. Record alcohol use on the liver event alcohol intake case report form.

5.5.1.2. Liver Event Adjudication Committee

A liver safety panel will be used to evaluate all participants who meet liver stopping criteria. Uniform sets of data and standards for adjudication will be applied across cases to inform outcomes. Full details of the analysis, timing, and the decision criteria will be pre-specified in an Adjudication Committee Charter.

5.5.1.3. Liver Chemistry Stopping Criteria – Restart/Rechallenge

Participants who meet liver toxicity stopping criteria should not be retreated with investigational product unless an exemption has been approved by the ViiV Safety and Labeling Committee (VSLC). The guideline for Rechallenge/Restart approved by the VSLC, which is maintained as a separate document (See Section 12.3, Appendix 3) must be followed.

5.5.1.3.1. Drug Restart/Rechallenge. Following Liver Events that are Possibly Related to IP

- Approval by the VSLC for drug restart or additional IM administration can be considered where:
- The participant is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If the restart/rechallenge is approved by the VSLC in writing, the participant must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Participants approved by the VSLC for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

5.5.1.3.2. Drug Restart Following Transient Resolving Liver Events Not Related to IP

Approval by the VSLC for drug restart or additional IM administration can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If restart/redosing of drug is approved by the VSLC in writing, the participant must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

- The participant must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.

Participants approved by the VSLC for restarting or re-dosing IP must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

See Section 12.3, Appendix 3 for full guidance.

5.5.2. QTc Stopping Criteria

A participant who has a QTc interval >550 msec considered causally related to IP will be withdrawn from the study. The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5 to 10 minute) recording period.

If an alternative cause of the QT prolongation is determined (e.g., participant receiving drug known to cause prolonged QT or TdP), the IP may be restarted (or continued) after consultation and agreement with the Medical Monitor.

The *same* QT correction formula *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, 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*. Safety ECGs and other non-protocol specified ECGs are an exception.

5.5.3. Virologic Failure

Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure.

5.5.4. Definition of Confirmed Virologic Failure

For the purposes of clinical management in this study, CVF is defined as:

Rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.

5.5.5. Managing Virologic Failure

Following study entry, no changes, or intensification of ART will be permitted prior to protocol-defined virologic failure, outside of the planned protocol regimens. Only

plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure. Baseline plasma HIV-1 RNA is the assessment completed on study Day 1. The definition of confirmed virologic failure does not apply to participants in the Long-Term Follow-Up Phase. These participants will be followed for the emergence of viral resistance.

Inadequate adherence is a common cause for virologic failure, and should be explored as a first step in the management of study participants (e.g., at the first indication of inadequate virologic response or rebound). Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as a suspected virologic failure, the Investigator should query the participant regarding intercurrent illness, recent immunization, or interruption of therapy.

5.5.5.1. HIV-1 RNA Blips

HIV-1 RNA "blips" are not usually associated with subsequent virologic failure [DHHS, 2015]. Although the implications of persistent HIV-1 RNA levels between the lower level of detection and <200 c/mL are unclear, the risk of emerging resistance is believed to be relatively low.

Participants with transient increases in HIV-1 RNA ('blips' HIV-1 RNA <200 c/mL) are not considered suspected virologic failures and do not require a change in therapy.

Participants who have a HIV-1 RNA ≥50 c/mL and < 200 c/mL at certain analysis timepoints (Week 48, Week 96) must return to the clinic as soon as possible (but no later than 4 weeks after the date of the Week 48 or Week 96 visit) for a repeat HIV-1 RNA test such that the result falls within the same analysis window.

In order to better characterize HIV-1 RNA 'blips,' if there is a known reason / explanation for the blip (e.g., immunization, allergies, etc), the study team should be notified of the reason and case context.

If the Investigator has concerns regarding persistent low level viremia (HIV-1 RNA ≥50 c/mL and <200 c/mL), the Medical Monitor should be contacted to discuss participant management. Following discussion with the Medical Monitor, additional viral load testing may be performed between visits to determine the appropriate participant disposition for the next scheduled visit

5.5.5.2. Suspected Virologic Failure

Upon notification that a participant's HIV-1 RNA plasma level meets the definition of virologic failure, the Investigator should confirm the definition is met by initiating a repeat of the HIV-1 RNA assessment.

The following guidelines should be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled within 2 to 4 weeks following resolution of any intercurrent illness, during which time the participant should receive full dose of all IP.

- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the participant should receive full dose of all IP.

- If therapy is interrupted* due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dose of all IP.

- The participant should have received full dose of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

*Note: treatment interruption guidelines above may not apply for participants on CAB LA + RPV LA treatment. The study team should be contacted to discuss any treatment interruptions for participants meeting the definition of virologic failure.

In addition, the Investigator should query the participant regarding intercurrent illness, recent immunization, or interruption of therapy.

Sites should contact the Medical Monitor to discuss individual participants, whenever necessary.

5.5.5.3. Confirmed Virologic Failure

Participants who confirm virologic failure must be discontinued from the study. However, participants who have received at least one dose of CAB LA or RPV LA prior to confirming virologic failure will remain in the study on oral HAART in the Long-Term Follow-Up Phase (see Section 4.2.4).

A plasma sample from the suspected virologic failure visit as well as Day 1 (Baseline) will be sent for genotypic and phenotypic resistance testing and the result made known to the Investigator when available. A plasma sample from the confirmation visit will be obtained for storage. This sample may be used for possible future analyses, e.g., for genotypic and phenotypic analyses of participants who experience virologic failure. See Section 7.8 for additional details for viral genotyping and phenotyping.

For all participants who meet CVF, baseline and suspected virologic failure plasma samples with HIV-1 RNA level ≥200 c/mL will be analyzed in an attempt to obtain genotype/phenotype data on as many samples as possible. Plasma samples for storage will also be obtained at unscheduled visits including confirmation of CVF. Participants may continue to receive study drug at the discretion of the investigator until results of resistance testing are available at which time the participant must be discontinued from the study. Even if genotype/phenotype data cannot be generated, participant must also be discontinued from the study.

If a participant is prematurely discontinued from the study, the investigator must make every effort to perform the Withdrawal Visit evaluations outlined in the Time and Events Section 7.1. These data will be recorded as they comprise essential evaluations needed to be done before discharging any participant from the study.

5.6. Participant and Study Completion

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

Study Completion

Participants are considered to have completed the study if they remain on therapy (i.e., have not permanently discontinued IP) and satisfy one of the following:

- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including the Week 52 visit, and did not enter the Extension Phase;

- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including the Week 52 visit, and entered and completed the Extension Phase (defined as remaining on study until commercial supplies of CAB LA + RPV LA become locally available or development of CAB LA + RPV LA is terminated or participant rolls over into ATLAS 2M).

Participants who withdraw from CAB LA + RPV LA and go into the Long-Term Follow-Up Phase will be considered to have prematurely withdrawn from the study, even if they complete the 52 week follow-up phase.

In addition to the 52 week Follow-Up phase required for participants randomized to CAB LA + RPV LA, an in-clinic Follow-Up visit will be conducted approximately 4 weeks after the last dose of study medication for participants randomized to current ART with ongoing AEs, and serious adverse events (SAEs) and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit. Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality). Follow-Up visits are not required for successful completion of the study.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the participant as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Investigational product (IP) in this protocol refers to the investigational study drugs Oral Cabotegravir, Cabotegravir LA, Oral Rilpivirine and Rilpivirine LA. These will be supplied by GlaxoSmithKline/ViiV Healthcare and Janssen Pharmaceuticals, respectively.

Participants randomly assigned to remain on their current ART will not have drug provided as clinical trial material. Current ART will be recorded on the Concomitant Antiretroviral Therapy (ConART) eCRF page.

The contents of the labels will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorised site staff. Investigational product and background NRTIs must be dispensed or administered only to participants enrolled in the study and in accordance with the protocol. For further details on IP storage, access, and administration refer to SPM.

6.1.1. Formulations of CAB + RPV

6.1.1.1. Cabotegravir Tablets (CAB)

CAB is manufactured by GlaxoSmithKline and is formulated as white to almost white oval shaped film coated 30 mg tablets for oral administration, packaged in high density polyethylene (HDPE) bottles with desiccant and child-resistant closure that include an induction seal. CAB tablets will be packaged in bottles of 30 tablets. Participants must keep all IP in its original pack container. GSK will notify sites if and when data are available to support the use of pill boxes. CAB tablets are to be stored up to 30°C [86°F] and protected from moisture.

CAB Tablet is composed of cabotegravir sodium, lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, magnesium stearate, and white film-coating. The white film-coating contains hypromellose, titanium dioxide and polyethylene glycol.

6.1.1.2. Rilpivirine Tablets (RPV)

RPV [Edurant® Product Information, 2015] is provided by Janssen Research & Development, LLC, a division of Janssen Pharmaceuticals, as 25 mg tablets that are off-white, round, biconvex, film-coated and debossed on one side with “TMC” and the other

side with "25". RPV is manufactured by Janssen -Cilag S.p.A, Latina, Italy. RPV will be provided as a globally marketed product which includes approvals in the US and the European Union. RPV will be overlabeled and packaged in bottles of 30 tablets. RPV tablets should be stored at 25°C (excursions permitted to 15°-30°C [59°-86°F]) and protected from light.

Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of RPV. Each tablet also contains the inactive ingredients croscarmellose sodium, lactose monohydrate, magnesium stearate, polysorbate 20, povidone K30 and silicified microcrystalline cellulose. The tablet coating contains hypromellose 2910 6 mPa.s, lactose monohydrate, PEG 3000, titanium dioxide and triacetin.

6.1.1.3. Cabotegravir Injectable Suspension (CAB LA)

CAB LA (GSK1265744 LA) is manufactured by GlaxoSmithKline and is a sterile white to slightly pink suspension containing 200 mg/mL of GSK1265744 as free acid for administration by intramuscular (IM) injection. The product is packaged in a 3 mL USP Type I glass vial with a 13 mm gray stopper and aluminium seal. Each vial is for single-dose use containing a withdrawable volume of 2.0 mL, and does not require dilution prior to administration. CAB LA injectable suspension is to be stored at up to 30°C, do not freeze.

CAB LA is composed of cabotegravir free acid, polysorbate 20, polyethylene glycol 3350, mannitol, and water for injection.

6.1.1.4. Rilpivirine Injectable Suspension (RPV LA)

RPV LA (also named JNJ-16150108-AAA), 300 mg/mL Extended Release Suspension for Injection (G001), is provided by Janssen Research & Development, LLC, a division of Janssen Pharmaceuticals, as a sterile white suspension containing 300 mg/mL of RPV as the free base. The route of administration is by intramuscular (IM) injection. RPV LA is packaged in a single use 4 mL USP Type I glass vial with a 13 mm grey stopper and aluminum seal. Each vial contains a nominal fill of 2.0 mL, and does not require dilution prior to administration. RPV LA injectable suspension should be kept in the outer package and stored at 2-8°C (do not freeze). RPV should also be protected from light.

RPV LA is composed of RPV free base, poloxamer 338, sodium dihydrogen phosphate monohydrate, citric acid monohydrate, glucose monohydrate, sodium hydroxide, water for injection.

6.2. Treatment Assignment

Informed consent must be obtained prior to any study procedures, including Screening visit activities. Participants will be assigned to study treatment in accordance with the randomization schedule. The randomization schedule, including stratification, will be generated using the GSK validated randomization software RANDALL NG. The randomization schedule is comprised of a series of blocks, with equal treatment allocation within each block, which are shared across centres via central randomization.

Given the open-label study design, central randomization was used to eliminate selection bias due to foreknowledge of randomized treatment. With central randomization, knowledge at a site of the randomized treatment group for previous subjects does not predict which treatment group will be assigned to the next randomized subject.

Randomization and study treatment assignment will be facilitated by the interactive response technology (IRT) through the central Randomization and Medication Ordering System Next Generation (RAMOS NG).

Following confirmation of fulfilment of study entry criteria, study site personnel will be required to register participants using RAMOS NG for assignment of a unique identifier (designating the participant's randomization code and treatment sequence assignment) for each participant participating in the study. A unique treatment number will be assigned for each participant participating in the study. Participants will be randomized in a 1:1 ratio to CAB + RPV or to remain on their current ART through Week 52, in accordance with the computer generated randomization schedule.

Participants who successfully complete 52 weeks of treatment and have a viral load <50 c/ml at Week 48 (or upon retest by Week 52) will be given the opportunity to enter the extension phase in which they will receive CAB LA + RPV LA. In addition, RAMOS NG will facilitate the initial supply and subsequent resupply of IP to study sites.

6.3. Dosage and Administration

Participants will be randomly assigned to receive treatment with Oral CAB 30 mg + RPV 25 mg once daily for 4 to 5 weeks during the Oral Phase, followed by CAB LA 600mg + RPV LA 900mg IM at Week 4b, CAB LA 400mg + RPV LA 600 mg IM at Week 8 and Q4 weekly thereafter, or to remain on their current ART. Regardless of treatment arm assignment, the investigator should instruct all participants on the importance of treatment adherence. This study has an open-label design. Dosing is outlined in Table 5 below.

Table 5 Dosage and Administration

Maintenance Phase (Day 1 to Week 52)	
CAB LA + RPV LA Arm	
Oral Lead-In	
Day 1 to Week 4b (2 tablets once daily)	Take 1 tablet CAB 30 mg once daily. Take 1 tablet RPV 25 mg once daily. *Should be taken together once daily at approximately the same time each day, with a meal.*
First Injections (Loading Dose) – Week 4b^	
Week 4b (two 3mL injections once)	Receive last dose of oral CAB + RPV regimen Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Maintenance Injections – every 4 Weeks (Q4W) following Week 4b	
Week 8 to Week 52 (two 2mL injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
Current ART Arm*	
Day 1 to Week 52 (Tablets once daily)	Take 2 NRTIs + INI **or** 2 NRTIs + NNRTI **or** 2 NRTIs + PI according to approved labeling. *Take Day 1 dose after randomization
Extension Phase (Week 52 through End of Study)	
CAB LA + RPV LA Arm – continue IM dosing every 4 Weeks+	
Current ART Arm (Transition to CAB LA + RPV LA)	
Oral Lead-In	
Week 52 to Week 56b (2 tablets once daily)	Take 1 tablet CAB 30 mg once daily. Take 1 tablet RPV 25 mg once daily. *Should be taken together once daily at approximately the same time each day, with a meal.*

First Injections (Loading Dose) – Week 56b^	
Week 56b (two 3mL injections once)	Receive last dose of oral CAB + RPV regimen Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Maintenance Injections – every 4 Weeks (Q4W) following Week 56b	
Week 60 forward (two 2 mL injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection

+Until locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of CAB LA or RPV LA is terminated
*Participants randomized to current ART will be given an option to switch to CAB LA + RPV LA (or be discontinued from the study) at Week 52. If the participant decides not to continue participation in the study, any arrangements for off-study ART should be made in advance of this Week 52 visit.
^See Section 6.6.1 for Dosing Considerations for CAB LA + RPV LA

The CAB + RPV oral regimen should be administered together once daily at approximately the same time each day with a meal.

6.4. Blinding

This will be an open-label study and therefore no blinding is required. No summaries of the study data according to actual randomized treatment groups will be available to sponsor staff prior to the planned Week 48 primary analysis.

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6. Preparation/Handling/Storage/Accountability

In accordance with local regulatory requirements, the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records). The amount of IP dispensed and/or administered to study participants, the amount returned by study participants, and the amount received from and returned to GSK must be documented.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

IP accountability will be evaluated using pill counts of unused IP for patients receiving oral treatment (oral CAB, oral RPV). This assessment will be conducted, when the participant completes oral CAB and RPV lead-in treatment in the Maintenance or Extension Phase, or any withdrawal that occurs during an oral treatment phase.

IP accountability for participants receiving CAB LA + RPV LA will be performed at the 'vial' level (e.g., correct number of vials were used for each injection). There may be a small amount of solution remaining in the vial which does not require quantification. Used vials may be discarded at the site once accountability is complete.

Product accountability records must be maintained throughout the course of the study.

- Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

6.6.1. Dosing Considerations for CAB LA + RPV LA

Vials of CAB LA and RPV LA are each supplied as a suspension and need no further dilution or reconstitution. Since RPV LA requires refrigeration, sites should allow the vial to come to approximately room temperature prior to injecting. The vials should be gently inverted a few times to re-suspend sediments and allow bubbles to subside, and then use a syringe to withdraw the required volume of suspension for IM injection.

All injections must be given intramuscularly in the gluteus medius. Sites may use their discretion as to where in the gluteus muscle each injection is given according to individual participant circumstance. If possible, injections should be spaced approximately 2 cm from one another, from the site of any previous injection or any injection site reaction. The time and location of injection will be captured in the eCRF.

IM injections should be administered at a 90 degree angle into the gluteus medius muscle using a needle of appropriate gauge and length (recommended 1.5" 23 gauge needle for CAB LA and a 1.5" 23 gauge needle for RPV LA in most participants). The needle should be long enough to reach the muscle mass and prevent study drug from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. Variable needle lengths and/or needles with different gauge (CAB LA: 21 to 25 gauge; RPV LA: 21 to 23 gauge) are permitted if needed to accommodate individual body types. Longer needle lengths may be required for participants with higher body mass indexes (BMIs, example > 30), to ensure that injections are administered intramuscularly as opposed to subcutaneously. BMI, needle gauge and length used will

be collected in the eCRF. Additional details of the injection device used by sites for IM administration including, but not limited to functional performance, may also be collected within the eCRF.

At the Week 4b visit, participants should be dosed with the IM regimen within 2 hours of taking the last oral regimen dose where possible. The same should apply to participants switching from the oral regimen to an IM regimen at Week 56b.

Should IM maladministration be suspected at any time (e.g., suspected under or overdose or inadvertent IV dosing), the investigator may consider requesting the participant stay onsite for approximately 2-3 hours post dose for safety monitoring and notifying the Medical Monitor. An ECG or any other supportive testing may be obtained at the discretion of the investigator. Additionally, a PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB and RPV plasma concentrations.

Additional dosing instructions and considerations can be found in the SPM

6.7. Compliance with Study Treatment Administration

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the participant's eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When participants self-administer oral study treatments at home, compliance with CAB + RPV dosing will be assessed through querying the participant during the site visits and documented in the source documents and CRF. IP accountability will be evaluated using pill counts of unused IP (CAB and RPV tablets). This assessment will be conducted each time the participant receives a new (refill) supply of oral study medication, completes the oral lead-in or any oral bridging phase. A record of the number of CAB and RPV tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will also be recorded in the eCRF.

Due to the long acting nature of the CAB LA and RPV LA it will be imperative that the participant is compliant with dosing instructions. As part of the screening and participant selection process, it is imperative that Investigators discuss with potential participants the long-term commitments for the trial, and the importance of adhering to treatment regimens. Sites are to have plans in place for adherence counselling for both treatment arms of the study for the duration of the study including the Long-Term Follow-Up Phase. In addition, Investigators must have plans in place to perform visit reminders, utilizing patient trackers provided by the study team as needed, and to verify the participant's contact information at each visit. Investigators should contact patients directly in the event that a participant misses any scheduled visit.

6.8. Protocol Permitted Substitutions

6.8.1. Oral Bridging

In exceptional circumstances, to address pre-planned missed CAB LA + RPV LA dosing visits, in consultation with the medical monitor, Investigators may provide daily oral CAB 30 mg and RPV 25mg as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. In certain circumstances (e.g., prior to steady state dosing and following a >4 week oral bridge) repeating the loading doses of CAB IM and RPV IM may be required. Should a participant require "oral bridging", sites must contact the medical monitor for guidance with treatment and dosing strategies prior to a missed CAB LA + RPV LA dose.

6.9. Interruption of Study Treatment and Visit/Dosing Windows

IP or current ART may be interrupted at the discretion of the Investigator in the event of an AE, according to the severity of the AE.

If one or more antiretroviral medications is held due to toxicity or adverse events, all antiretroviral medications must be held to reduce the risk of development of resistance taking into account both the length of the planned interruption and the pharmacokinetic half-life of each antiretroviral of the regimen, in a way to minimize the risk of development of resistance.

It is important to note that keeping to the participant's visit schedule is a very important component to the study.

Note: **All decisions regarding dose interruption / resumption must be discussed with the medical monitor in advance.**

6.9.1. IM Dosing

Participants receiving CAB LA and/or RPV LA are anticipated to be at risk for development of virologic resistance if ART is interrupted. The time period during which participants are at risk for development of virologic resistance may be determined by the period between when drug levels fall below therapeutic values and when they fall below levels which exert selective pressure on HIV. This time period will vary by ART agent and is dependent upon effective concentration, inhibitory concentration, and half-life. Plasma concentrations of both LA drugs may be measurable for more than one year following IM injections. Any interruption in IM dosing should be discussed with the Medical Monitor. Investigators should ensure that the participant initiates alternative highly active ART to minimize the risk of developing resistance as concentrations of CAB and RPV decline over time.

IM dosing is expected to occur during the week in which the participant's projected visit falls (as according to the date of the first injection). The first injections are administered at Week 4b (can be performed as soon as lab results from Week 4a become available), and the second injections are given at Week 8. The dosing window for the second injections allows administration between Week 7 and Week 8, but not later than Week 8. The dosing window for the third injections allows administration between Week 11 and

Week 12 but not later than Week 12. For subsequent injection visits, an additional (+ or -) 7 day window, from the projected visit date, is allowable for IM dosing but also not preferred. In addition, starting after the Week 12 injection, efforts should be made to limit time between injection visits to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds or is projected to exceed 5 weeks. For the duration of the study, the injection visit schedule should be maintained according to the first IM injections given at Week 4b.

For participants transitioning from current ART to IM dosing, the first injections are administered at Week 56b (can be performed as soon as lab results from the 56a visit become available), and the second injections are given at Week 60. The dosing window for the second injections allows administration between Week 59 and Week 60, but not later than Week 60. The dosing window for the third injections allow administration between Week 63 and Week 64, but not later than Week 64. For subsequent visits, a (+ or -) 7 day window, from the projected visit date, is allowable for IM dosing but also not preferred.

At the one-week post dose visits (Week 5 and Week 41), there is no defined visit window, rather visits should occur approximately one week from the last injection.

- Dosing may occur without consultation from the Medical Monitor if performed within the (+ or -) 7 day window.
- Any request for the visit/dosing to occur outside of the allowed window must be discussed and agreed with the Medical Monitor *prior* to dosing. In the event of a late dose, a revised dosing schedule for subsequent dosing may be required and will be communicated to the site staff at the time of approval for continued dosing. Temporary switch to oral dosing of CAB and/or RPV may be an option based on individual participant circumstance as described in Section 6.8.
- See the SPM for scheduling guidance and further information and examples.

Note: **All decisions regarding dose interruption/ resumption must be discussed with the Medical Monitor in advance.**

6.9.2. Oral Dosing

Visits for participants on the oral dosing arm are expected to occur as projected according to the Baseline visit. There is a (+ or -) 3 day visit window, from the projected visit date. However, the number of tablets dispensed should be considered when scheduling the next visit.

Any interruption in therapy (scheduling conflicts, life circumstances, etc) during any oral dosing period that is greater than 7 consecutive days must be discussed with the Medical Monitor prior to resumption of therapy. The Medical Monitor must be contacted upon site staff becoming aware of resumption in therapy, if therapy was resumed without prior approval.

Visits for participants in Long Term Follow Up are expected to occur as projected according to the last injection.

6.10. Discontinuation of Study Treatment

Participants unable to manage drug toxicity or tolerate investigational product (IP, either formulations of CAB or RPV) must have IP discontinued. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART enter the Long-Term Follow-Up Phase for 52 weeks of follow up (see Section 4.2.4).

6.11. Treatment of Study Treatment Overdose

For participants receiving Oral CAB, any tablet intake exceeding a total daily dose of 30 mg will be considered an overdose. For participants receiving oral RPV, any dose exceeding a total daily dose of 25 mg will be considered an overdose.

For CAB LA and RPV LA, any single dose in excess of the studied doses will be considered an overdose.

Should IM maladministration, specifically overdose or inadvertent IV dosing, be suspected at any time, the participant will stay onsite for approximately 2-3 hours post dose for safety monitoring and an ECG will be performed at 2 hours post dose. The Medical Monitor will be notified in the event of a suspected maladministration.

In the event of suspected maladministration, additional PK samples will be drawn at 2 hours post dosing for evaluation of CAB and RPV concentrations.

For the purposes of this study, an overdose is not an AE (refer to Section 12.6.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a SAE (see Section 12.6.2).

If an overdose occurs and is associated with an adverse event requiring action, all study medications must be temporarily discontinued until the adverse event resolves.

The Investigator should use clinical judgement in treating overdose, as ViiV Healthcare is unable to recommend specific treatment.

In the event of an overdose the investigator or treating physician should:

1. Contact the Medical Monitor immediately
2. Closely monitor the participant for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until the IP can no longer be detected systemically (at least 5 days for oral CAB and oral RPV, and 52 weeks for CAB LA and RPV LA
3. Obtain a plasma sample for pharmacokinetic (PK) analysis if possible within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.12. Treatment After the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study treatment. Participants who have successfully completed 96 weeks of treatment will continue to have access to both CAB LA and RPV LA in the Extension Phase until study treatment is either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated.

6.13. Concomitant Medications and Non-Drug Therapies

Participants must be advised to notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications. Concomitant medications (prescription and non-prescription) will be permitted during the course of the study at the investigator's discretion (except for prohibited medications described in Section 6.13.2) and should be administered only as medically necessary during the study. All concomitant medication, blood products, and vaccines taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name, route, and the dates of administration are to be recorded.

6.13.1. Permitted Medications and Non-Drug Therapies

Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of plasma HIV-1 RNA, it is recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn. This approach will minimize the risk of non-specific increases in the level of plasma HIV-1 RNA at the next scheduled assessment.

Other IM injectables (with exceptions below) are permitted but must be administered away from the site of IP administration (should be spaced 2 cm or more away from site of IP injection).

Antacid and H2 Antagonist Use:

While both oral CAB and RPV have dosing requirements with antacid products containing divalent cations, only oral RPV has requirements for dosing with H2

antagonists. Since co-administration of oral CAB and RPV is required in this study, the most restrictive dosing requirements must be taken into consideration.

CAB oral administration only: Antacid products containing divalent cations (e.g., aluminium, calcium and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB.

Concurrent administration of multivitamins is acceptable.

RPV oral administration only: Antacid products containing divalent cations (e.g., aluminium, calcium and magnesium) must be taken at least 2 hours before or at least 4 hours after RPV. H2-Receptor antagonists (e.g. cimetidine, famotidine, nizatidine, ranitidine) may cause significant decreases in RPV plasma concentrations. H2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after RPV. RPV should not be co-administered with proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.

RPV: Administration of clarithromycin, erythromycin and telithromycin is not recommended with RPV due to possible increase in plasma concentration of RPV due to CYP3A enzyme inhibition. Where possible, alternatives such as azithromycin should be considered. Please refer to the local rilpivirine prescribing information for guidance regarding other drugs that are prohibited, should be used with caution, require dose adjustment, or increased clinical monitoring if taken with rilpivirine.

Drugs that cause Torsade des Pointes (TdP) should be used with caution when on rilpivirine (see SPM for list of drugs associated with TdP).

6.13.2. Prohibited Medications and Non-Drug Therapies

The following concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Exclusion Criteria #32, Section 5.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SPM). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Acetaminophen (paracetamol) cannot be used in patients with acute viral hepatitis (James, 2009).
- Chronic use of systemic (oral or parenteral) glucocortioids must be avoided due to their immunosuppressive effect and potential decreases in RPV plasma concentrations; however, short treatment courses with oral prednisone/ prednisolone/methylprednisolone (e.g. adjunctive treatment of Pneumocystis pneumonia with ≤ 21 days of tapering prednisone) are allowed. A single dose of

systemic dexamethasone is permitted (more than a single dose in a treatment course may cause significant decrease in RPV plasma concentration and is prohibited). Topical, inhaled or intranasal use of glucocortioids will be allowed.

- Hepatitis C infection therapy is prohibited during the Maintenance Phase before the Week 48 primary endpoint, and interferon-based HCV therapy or use of any drugs that have a potential for adverse drug:drug interactions with study treatment is prohibited throughout the entire study.

For information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy in the regimen, please consult the local prescribing information.

6.13.2.1. Concurrent with CAB and/or RPV

For participants receiving **either formulation** of CAB and/or RPV, the following medications could significantly decrease the levels of CAB and/or RPV due to enzyme induction and therefore must not be administered concurrently:

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampicin / Rifampin
- Rifapentine
- St. John's wort (*Hypericum perforatum*)

Concurrent with RPV

In addition, participants must discontinue the following (or change to an allowable alternative) while receiving treatment with oral RPV:

- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole;
- systemic dexamethasone (more than a single dose, for both Oral RPV and RPV LA)

If the participant cannot discontinue use or change to an allowable alternative while receiving treatment with RPV, the participant should not be randomized into the study.

6.13.2.2. Concurrent with either CAB LA or RPV LA

In addition, for participants receiving CAB LA and RPV LA, use of anticoagulation agents for greater than 14 days is prohibited, with the exception of the use of anticoagulation for DVT prophylaxis (e.g., postoperative DVT prophylaxis) or the use of low dose acetylsalicylic acid (≤325mg). Systemic anticoagulation (including prophylaxis doses) on the day of an IM injection should be avoided.

Note: Any prohibited medications that decrease cabotegravir or rilpivirine concentrations should be discontinued for a minimum of four weeks or a minimum of three half-lives (whichever is longer) prior to the first dose and any other prohibited medications should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

6.13.2.3. Prohibited Medications for Participants Receiving Current Regimen

For participants randomly assigned to remain on their current ART, refer to local prescribing information for details regarding concurrent therapies.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 7.1).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

7.1. Time and Events Table

Note: While some assessments included in the Time and Events Table are conducted less frequently following the secondary endpoint (Week 96), IM injections for participants randomized to CAB LA + RPV LA (and for participants who switch to CAB LA + RPV LA during the Extension Phase) will continue to be administered Q4W. Beginning after Week 96, the schedule of assessments for all participants will be modified to collect clinical chemistries, HIV-1 RNA, and CD4+ cell count every 12 weeks.

From Week 60 forward, all participants (from both originally randomized treatment arms), will have the same schedule of events (same visits, same assessments, same time frame).

Procedure	Screening Visit[a]	Maintenance Phase											Extension Phase								Withdrawal	Follow-up Phase
		Week																				
		Baseline, Day 1	4A	4B[b]	5[b]	8, 12,16,20	24	28, 32, 36,40	41[b]	44	48	52	56A	56B[b]	60	64, 72, ,80, 88	68, 76, 84, 92	96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
Clinical and Other Assessments																						
Written informed consent	X																					
Eligibility Verification (Inclusion/Exclusion Criteria)	X	X[c]									X[c]											
Randomization		X																				
Demography	X																					

Procedure	Screening Visit[a]	Maintenance Phase											Extension Phase								Withdrawal	Follow-up Phase
		Week																				
		Baseline, Day 1	4A	4B[b]	5[b]	8, 12,16,20	24	28, 32, 36,40	41[b]	44	48	52	56A	56B[b]	60	64, 72, ,80, 88	68, 76, 84, 92	96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
Medical History[d]	X																					
Medication History/ Prior ART history	X																					
Symptom Directed Physical Exam and Medical Assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, Height and BMI[f]		X									X			X				X			X	
Cardiovascular risk assessment	X	X																				
Vital Signs (BP, HR,Temperature)[g]	X	X									X			X				X			X	
12-lead ECG [h]	X	X pre-dose x3		X							X			X				X			X	

Procedure	Screening Visit[a]	Maintenance Phase										Extension Phase								Withdrawal	Follow-up Phase
		Baseline, Day 1	Week																		
			4A	4B[b]	5[b]	8, 12,16,20	24	28, 32, 36,40	41[b]	44	48	52	56A	56B[b]	60	64, 72, ,80, 88	68, 76, 84, 92	96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
CDC HIV-1 classification	X	X																				
HIV Associated Conditions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs, SAEs, Concomitant Medications	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISR Assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Columbia Suicide Severity Rating Scale (eC-SSRS) [j]	X	X	X			X	X	X		X	X				X	W 72	W 84	X			X	
Clinical chemistry and Hematology	X	X	X			X	X	X		X	X	X	X		X	X		X		X	X	X
Rapid Plasma Reagin (RPR)	X	X																				
Pregnancy Testingk	SR	UR	SR	UR		SR	SR	SR		SR	SR	SR	SR	UR	SR	SR	SR	SR	SR	SR	SR	SR

Procedure	Screening Visit[a]	Maintenance Phase											Extension Phase								Withdrawal	Follow-up Phase
		Week																				
		Baseline, Day 1	4A	4B[b]	5[b]	8, 12,16,20	24	28, 32, 36,40	41[b]	44	48	52	56A	56B[b]	60	64, 72, ,80, 88	68, 76, 84, 92	96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
HIV-1 RNA and sample for storage[l] (S)=Storage only	X	X		X		X	X	X		X	X	S		X	X	X		X		X	X	X
CD4+ cell count	X	X		X		X	X	X		X	X	X		X	X	X		X		X	X	X
CD8+ cell count		X		X			X				X			X				X			X	
Urinalysis[m]		X	X				X				X		X					X			X	
Fasting Lab Assessments: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides[n]		X									X							X			X[o]	

Procedure	Screening Visit[a]	Maintenance Phase											Extension Phase								Withdrawal	Follow-up Phase
		Baseline, Day 1	Week																			
			4A	4B[b]	5[b]	8, 12,16,20	24	28, 32, 36,40	41[b]	44	48	52	56A	56B[b]	60	64, 72, ,80, 88	68, 76, 84, 92	96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
Hepatitis B (HBsAg), Anti-HBc, and Anti-HBsAG, Hepatitis C (anti-HCV Ab)	X																					
HLA-B*5701	X																					
PT/PTT/INR	X	X																				
Renal, bone, marker analytes (blood/urine)[p]		X									X							X			X	
PBMCs[q]		X																X			X	
Genetics sample[r]		X																				

Procedure	Screening Visit[a]	Maintenance Phase											Extension Phase								Withdrawal	Follow-up Phase
		Week																				
		Baseline, Day 1	4A	4B[b]	5[b]	8, 12,16,20	24	28, 32, 36,40	41[b]	44	48	52	56A	56B[b]	60	64, 72, ,80, 88	68, 76, 84, 92	96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
Pharmacokinetics – CAB + RPV only																						
PK sampling[s] (S)=Storage only				X	X	X	X	X	X	X	X	X		X	X	S		X			X	S
Investigational Products																						
Oral CAB and Oral RPV Dispensation[t]		X	X									X	X									
IP accountability (Pill Counts)			X	X									X	X								
IM treatment administration[u]				X		X	X	X		X	X	X	X	X	X	X	X	X	X	X		

Procedure	Screening Visit[a]	Maintenance Phase											Extension Phase								Withdrawal	Follow-up Phase
		Week																				
		Baseline, Day 1	4A	4B[b]	5[b]	8, 12,16,20	24	28, 32, 36,40	41[b]	44	48	52	56A	56B[b]	60	64, 72, ,80, 88	68, 76, 84, 92	96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
Patient Reported Outcomes[v]																						
HAT-QoL (short-form)		X					X				X							X			X	
SF-12		X					X				X							X			X	
HIV TSQs		X		X			X			X								X			X	
HIV TSQc[w]											X										X	
ACCEPT		X				X Wk8 only	X				X							X			X	
Reason for Switch[x]		X										X										
Preference[y]											X							X				
NRS[z]				X	X			X Wk40 only	X										X				
PIN					X				X		X							X			X	

Procedure	Screening Visit[a]	Maintenance Phase										Extension Phase								Withdrawal	Follow-up Phase
		Week																			
		Baseline, Day 1	4A	4B[b]	5[b]	8, 12,16,20	24	28, 32, 36,40	41[b]	44	48	52	56A	56B[b]	60	64, 72, ,80, 88	68, 76, 84, 92	96	Every 4 Weeks After Week 96	Every 12 Weeks After Week 96		
Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the participant has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.																					

a. Complete all Screening assessments within 35 days. Participants may begin the Maintenance Phase as soon as all Screening assessments are complete. Participants may be rescreened once and will be assigned a new participant number. HLA-B*5701 result is not required to inform eligibility status.
b. Visits at Weeks 4b, 5, 41, and 56b are only for participants randomized to CAB LA + RPV LA or transitioning from current ART to CAB LA + RPV LA during the Maintenance or Extension Phase, respectively.
c. Confirmation of eligibility to enter the Maintenance Phase (Section 5), and eligibility to enter the Extension Phase (Section 4.2.3).
d. Collect full routine medical history plus (report at Baseline visit): HIV risk factors (may be collected at a later study visit), cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal, bone, and neurologic disorders.
e. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for participants management and/or care of participant.
f. Height collected at Baseline only.
g. Measure vital signs after about 5 minutes of rest in a semi-supine position.
h. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes. ECGs will be performed pre-dose. ECG will be performed in triplicate at Baseline (Day 1). In addition to a pre-dose ECG, a 2 hour post-dose ECG will be performed at Weeks 4B and Week 48 for subjects randomized to CAB LA + RPV LA only.
i. Only SAEs related to study participation or to a concomitantly administered ViiV/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
j. On Day 1, the eC-SSRS is to be administered prior to randomization. The eC-SSRS will be administered at each Q4W injection visit through the Week 48 primary endpoint, followed by Q12W thereafter through Week 96 (Week 60, 72, 84, 96). The eC-SSRS will preferably be completed at the beginning of the visit following administration of other PROs required prior to injections.
k. Women of childbearing potential only. SR=serum, UR=urine. Pregnancy events will be captured starting at Day 1 following exposure to study drug. Serum pregnancy test can substitute for urine pregnancy test if locally required but must be appropriately timed to confirm pregnancy status prior to randomization and first IM administration.
l. HIV-1 RNA will not be collected for analysis at Week 52 and Week 100 (Week 48 or Week 96 retest will be captured as unscheduled visit). Plasma for storage will be collected at Week 52 and Week 100. Plasma for storage samples will be used for possible future analyses

m. A morning specimen is preferred. To assess biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
n. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
o. Only collect if the Withdrawal visit occurs at Week 48, or 96.
p. Blood sample for renal and bone biomarker assessments: **Renal:** Cystatin C; Retinol Binding Protein (RBP);.**Bone:** bone specific alkaline phosphatase, procollagen type 1-N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D
q. Whole blood/PBMC collection samples may be used for virologic analyses as described in Section 7.8. PBMCs will be collected at Day 1, Week 96, and Withdrawal if prior to Week 96.
r. Informed consent for genetic research must be obtained before sample collection
s. One blood sample for CAB and RPV each to be collected at each PK timepoint. PK samples are to be collected pre-dose during visits requiring IM administration. 2 hour post dose samples also taken at Weeks 4b, 48, 56b, and 96. Pre-dose samples at Weeks 56b, 60, and 2 hour post-dose sample at Week 56b are only for subjects transitioning from Current Art arm to CAB LA + RPV LA. Pre-dose samples are to be collected after review of PK diary at Week 4b and 56b and prior to the final oral dose of CAB + RPV. Additionally PK samples will be taken during the 1 week post-dose Week 5 and 41 visits. PK window allowed for sample collection; includes 3 to 10 days for 1 wk post dose sample (Visits 5 and 41); ±one hour for 2 hour post dose sample (Weeks 4b, 48, 56b, and 96). See Section 7.5.1 for details of PK sampling schedule.
t. Only for Participants entering CAB + RPV Oral Treatment
u. Participants switching to CAB LA + RPV LA will take final dose of oral lead-in regimen in the clinic at The Week 4b visit or Week 56b and begin injections. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. The first injection can be performed as soon as central lab results become available and safety parameters are reviewed.
v. With the exception of the NRS questionnaire, all Patient Report Questionnaires/Surveys are recommended to be administered via validated electronic site pad or paper instrument at the beginning of the visit before any other assessments are conducted and prior to administration of the eC-CSSRS. NRS is to be given post injection. Conduct questionnaires/surveys at Withdrawal if occurring prior to Week 96.
w. HIV TSQ (c) to be administered at Week 48 to LA injection arm only
x. "Reason for switch" will be administered prior to randomization at Day 1. At Week 52, "Reason for Switch" will be given only to participants randomized to the "Current ART" arm.
y. Preference" question to be administered at Week 48 to patients randomized to CAB LA + RPV LA arm, and at Week 96 to patients randomized to the "current ART arm" who switched to CAB LA + RPV LA at the end of maintenance phase.
z. NRS will be administered on injection visits approximately 30-60 minutes following injections. Participant should record the maximum level of pain experienced with the most recent injections.

Note: BP – Blood pressure, HR – Heart Rate, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, PT Prothrombin Time, PTT Partial Thromboplastin Time, INR International normalized ratio

7.2. Screening and Critical Baseline Assessments

Written informed consent must be obtained from each potentially eligible participant by study site personnel prior to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). After signing an informed consent, participants will complete Screening assessments to determine participant eligibility. Each participant being screened for study enrolment evaluation will be assigned a participant number at the Screening visit. This number will be given sequentially in chronological order of participant presentation according to a numeric roster provided by GSK.

7.2.1. Screening Assessments

Eligibility criteria must be carefully assessed at the Screening visit. Physical examinations should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Background information to be collected at Screening includes demography and prior ART history.

Eligible participants may be randomly assigned immediately as soon as all Screening assessments are complete and the results are available and documented. All participants will complete the screening period of approximately 14 days prior to Baseline (Day 1) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. The Screening period may be extended to 35 days to accommodate availability of all Screening assessment results, completion of source document verification to satisfy the Inclusion and Exclusion Criteria, and scheduling. All Screening results **must** be available prior to randomization.

All information about the participant's current regimen must be available for review by the Principal Investigator or designee prior to randomization. Source documents from other medical facilities must be located/received during the 14 day (up to 35 days) screening period and under no circumstances may the participant be randomized in the absence of source documentation even if there are delays in receipt of this information.

Any available prior genotypic resistance testing must be provided to GSK, after screening and before randomization according to guidance in the SPM, to provide direct evidence of no pre-existing exclusionary resistance mutations. The lack of exclusionary resistance mutations must be confirmed by the study virologist, which will be provided before the screening window closes. Details on use of RAMOS for tracking historic resistance report availability and submission to ViiV Healthcare Virology for evaluation are described in the SPM. Details regarding baseline or prior resistance data must be noted in the source documentation.

Participants infected with HBV will not be enrolled in the study. Evidence of HBV infection is based on the results of testing at Screening for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs), and HBV DNA. HBV DNA will only be performed for participants with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).

Participants with an anticipated need for HCV therapy during the study must not be enrolled into this study, as HCV therapy currently includes the prohibited medication interferon. The length of this study should be considered when assessing the potential need for therapy.

Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF.

All participants will be screened for syphilis (rapid plasma reagin [RPR]) at Screening. Participants with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded. Participants with a serofast RPR result despite history of adequate therapy and no evidence of re-exposure may enrol after consultation with the Medical Monitor. Participants with a positive RPR test who have not been treated may be rescreened at least 30 days after completion of antibiotic treatment for syphilis.

The eCSSRS (see Section 7.4.5) assessed at the Screening visit will assess the participant's lifetime risk (any suicidal ideation, behavior, etc occurring over the participant's lifetime). A positive alert (indicating some risk) is not necessarily exclusionary, rather a means to assess overall risk.

Participants who meet all entry criteria are randomized and assigned a randomization number. A single repeat of a procedure/lab parameter is allowed to determine eligibility (unless otherwise specified). Participants not meeting all inclusion and exclusion criteria at initial screen may be rescreened and receive a new participant number one time unless they were excluded for reason of having exclusionary historic genotypic resistance. Participants who are randomized into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

7.2.2. Baseline Assessments

At Day 1 and prior to randomization, any changes to the eligibility parameters must be assessed and any results required prior to randomization (e.g., Day 1 urine pregnancy test for women of childbearing potential) must be available and reviewed. The following demographic parameters will be captured: year of birth, sex, race and ethnicity. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

HIV-1 genotypic resistance testing and plasma HIV-1 RNA measurement results from Screening must be available prior to the Baseline visit.

Baseline information to be collected at Day 1 includes general medical history and current medical conditions. Laboratory and health outcomes assessments will also be assessed. Questionnaire/surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted, in the order specified. For participants who agree to the optional assessment, a whole blood sample for genetic research should be collected at Day 1.

In addition to a full routine medical history at Baseline, more detailed information will be collected for some disease processes such as:

- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at Baseline and assessments will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. In addition, medical history/risk factors for renal disease such as nephropathy, renal failure, and nephrolithiasis will be assessed.
- history of illicit drug use [e.g., cocaine, heroin, and methamphetamine use]);
- intravenous drug use history;
- gastrointestinal disease (e.g., GI bleeding, PUD, etc);
- metabolic (e.g., Type I or II diabetes mellitus);
- psychiatric (e.g., depression);
- renal (e.g., nephrolithiasis, nephropathy, renal failure); and,
- neurologic disorders

Procedures conducted as part of the participant's routine clinical management [e.g., laboratory assessments] and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.3. Efficacy

7.3.1. Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events schedule (Section 7.1). Methods to be used may include but are not limited to the Abbott RealTime HIV-1 Assay lower limit of detection (LLOD) 40 c/mL. In some cases (e.g., where the HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods will be used to further characterize HIV-1 RNA levels.

7.3.2. Lymphocyte Subsets, CD4+ and CD8+

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts, ratios) according to Time and Events schedule (Section 7.1) and Laboratory Assessments (Section 7.4.2).

7.3.3. HIV Associated Conditions

HIV-associated conditions will be recorded as per Time and Events schedule (Section 7.1). HIV-associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection (see Section 12.4).

7.4. Safety

7.4.1. Clinical Evaluations

The following clinical evaluations will be performed according to the Time and Events schedule:

- Monitoring and recording of all AEs and SAEs. Additional information on the Time Period and Frequency of Detecting AEs and SAEs is provided in Section 7.4.3.1.
- Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).
- Height and weight will be measured and recorded. Height collected on the Day 1 (Baseline) only.
- Vital signs will include systolic and diastolic blood pressure and heart rate collected after resting for about 5 minutes. Temperature will also be collected.
- Past medical history, family history, social history, medication history. Targeted history on cardiovascular risk (smoking history, family and personal history).
- HIV-associated conditions will be recorded.
- Electrocardiogram: A 12-lead ECG will be performed in a semi-supine position after 5 minutes of rest. On Day 1 (Baseline) of the Maintenance Phase, ECGs should be performed in triplicate prior to first dose. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each participant for the site. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations. The same QT correction formula 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.
- Regular monitoring of hematology, blood chemistry, urinalysis and fasting glucose and lipids (parameters to be tested listed below).
- Periodic assessment of glucose, insulin, and bone, cardiovascular, and renal markers;

- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of CAB LA or RPV LA or as required by the Medical Monitor following a treatment interruption(s). If serum testing is required locally, the results should be available prior to the visit where urine testing is indicated per the Time and Events Schedule (Section 7.1).
- Evaluation and documentation of all concomitant medications and blood products.
- Injection Site Reactions (ISRs) will be assessed clinically during the Maintenance and Extension Phases for the following:

  Pain, tenderness, pruritis, warmth, bruising, discoloration, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).
- A clinical assessment (using Division of Acquired Immunodeficiency Syndrome [DAIDS] grading scale) should be performed both before and after an injection to identify resolving and new ISRs. All injection site reactions are considered adverse events. The clinical assessment and interpretation of any ISR, will be documented in the ISR AE eCRF.
- Columbia Suicide Severity Rating Scale (eC-SSRS) will be assessed as per the Time and Events Schedule (see Section 7.1 and Suicidal Risk Monitoring Section 7.4.5).

Any appropriately qualified site personnel (e.g., Investigator, sub-Investigator, or study coordinator/nurse) can perform assessments.

7.4.2. Laboratory Assessments

All protocol required laboratory assessments, as defined in the Time and Events Schedule (see Section 7.1), must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labeled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF. Local laboratory services may be used to verify pending laboratory parameters only after consultation and agreement with the study team.

Refer to the lab manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Labs will be automatically graded by the central lab according to the DAIDS toxicity scales (See Section 12.2 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events").

For fasting laboratory assessments, an overnight fast is preferred; however, a minimum of a 6 hour fast is acceptable.

Table 6 includes lab parameters to be assessed as per the Time and Events Schedule (see Section 7.1):

Table 6 Safety Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[c]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine clearance[b]
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			
Plasma HIV-1 RNA[e]			
CD4+ and CD8+ cell counts [CD4/CD8 ratio][f]			
Peripheral Blood Mononuclear Cells (PBMCs): Day 1, Week 96, Withdrawal only			
Hepatitis B (HBsAg), anti-HBc, anti-HBsAg, and hepatitis C antibody (Screening)[g]			
Rapid Plasma Reagin (RPR) (Screening and Baseline)			
HLA-B*5701 (Screening only)			
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)			
Pregnancy test for women of childbearing potential[h]			
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate			
Genetics Sample			
Renal biomarkers including Cystatin-C (blood), Retinol Binding Protein (RBP, blood/urine)[i]			
Bone biomarkers including: Bone-specific alkaline phosphatase, procollagen type 1 N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D[i]			
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)			

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO2 = carbon dioxide, HDL = high density lipoprotein, LDL = low density lipoprotein, HBsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [Levey, 2009].
c) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
d) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
e) For participants meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain genotype/phenotype data.
f) CD8+ cells will only be reported at Baseline, Day 1, Weeks 4b, 24, 48, and 96.
g) HBV DNA will only be performed for participants with a positive anti-HBc and negative HBsAg and negative anti-

HBs (past and/or current evidence).

h) Urine pregnancy test/ serum pregnancy test will be performed according to the Time and Events Table (Section 7.1).

i) Since the intention is to utilize these biomarker data for research purposes, the sponsor will not be reporting the results of these assessments to the investigator, except for 25 hydroxy-vitamin D.

7.4.3. Adverse Events (AE) and Serious Adverse Events (SAEs)

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.3.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.3.1), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.6, Appendix 6
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.
- During the Extension Phase, AEs leading to Withdrawal and all SAEs will be recorded.

7.4.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.4.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.4) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 5.5). Further information on follow-up procedures is given in Section 12.6, Appendix 6).

7.4.3.4. Prompt Reporting of Serious Adverse Events and Other Events

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to the medical monitor as described in Table 7 once the investigator determines that the event meets the protocol definition for that event. Any seizure or suspected seizure should be reported in an expedited manner, as noted in Table 7.

Criteria for liver chemistry stopping and follow-up criteria are in Section 5.5.1.

Table 7 Reporting of Serious Adverse Events and Other Events

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow-up reports to be completed when the cardiovascular event or death is reported[a]	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow-up reports to be completed when the cardiovascular event or death is reported[a]	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 hours	"Pregnancy Notification Form"	Within 24 hours of investigator awareness of pregnancy outcome	"Pregnancy Follow-up Form" and SAE if required
Seizure or suspected seizure	24 hours	eCRF	24 hours	eCRF
Suspected ABC HSR in participants randomized to the current ART arm or receiving Oral SOC during the Long-Term Follow-Up Phase[b]	1 week	ABC HSR eCRF	1 week	Updated ABC HSR eCRF
ALT≥3×ULN **and** bilirubin≥2×ULN (>35% direct) (or ALT≥3×ULN)	24 hours[c]	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable[d]	24 hours	Updated "SAE" data collection tool/"Liver Event" documents[d]

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
ALT≥5×ULN that persists ≥2 weeks	24 hours[c]	Liver Event eCRFd	24 hours	Updated Liver Event eCRF[d]
ALT ≥8×ULN	24 hours[c]	Liver Event eCRF[d]	24 hours	Updated Liver Event eCRF[d]
ALT ≥3×ULN (if baseline ALT is <ULN) or ALT ≥3 fold increase from baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours[c]	Liver Event eCRF[d]	24 hours	Updated Liver Event eCRF[d]

a. Additional details and time frames for reporting supplementary information for cardiovascular and death events are provided in Section 7.4.3.7 and Section 7.4.3.8, respectively.
b. ABC HSR eCRF only required if event meets one of the ICH E2A definitions of seriousness.
c. GSK must be contacted at onset of liver chemistry elevations to discuss participant safety.
d. Liver event documents (i.e., "Liver Event eCRF" and updates, "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

The method of recording, evaluating, and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to the medical monitor are provided in the SPM. Procedures for post study AEs/SAEs are provided in the SPM. Primary and secondary Medical Monitor/SAE contact information is provided on the Medical Monitor/Sponsor Information Page of the current protocol.

7.4.3.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Disease related events (DREs) or outcomes listed in the CDC Classification System for HIV-1 Infections (Appendix 4) can be serious/life threatening and will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE. However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The investigator determines that the event or outcome qualifies as an SAE under part 'other situations' of the SAE definition (see Section 12.6.2), or
- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product, or

- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.

- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

If any of the above conditions is met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly (i.e., expedited reporting, see Section 7.4.3.4) to GSK.

7.4.3.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.3.7. Cardiovascular and Death Events

Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:

Myocardial infarction/unstable angina

Congestive heart failure

Arrhythmias

Valvulopathy

Pulmonary hypertension

Cerebrovascular events/stroke and transient ischemic attack

Peripheral arterial thromboembolism

Deep venous thrombosis/pulmonary embolism

Revascularisation

For any cardiovascular events detailed above, whether or not they are considered SAEs, and all deaths, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

7.4.3.8. Death Events

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the Division of Acquired Immunodeficiency Syndrome (DAIDS) toxicity scales (see Appendix 2). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 7.4.3.2. and Section 12.6.

7.4.3.9. Treatment Interruption Due to an Adverse Event

IP may be interrupted at the discretion of the investigator and according to the severity of the AE. If one or more ART medication is held due to toxicity or AEs, all ART medications should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each ART of the regimen, in order to minimize the risk of development of resistance.

No toxicity-related dose reductions of IP will be allowed. IP should be restarted as soon as medically appropriate; in general, for oral dosing, this should be no longer than 14 days after discontinuation (unless Grade 3 or 4 toxicities persist). Any interruption in therapy during the Maintenance Phase, oral dosing, of greater than 7 consecutive days must be discussed with and agreed by the Medical Monitor prior to resumption of therapy. The Medical Monitor must be contacted upon becoming aware of resumption in therapy, if therapy was resumed without prior approval (Section 6.9). **IM dosing is expected to occur during the week in which the participant's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window, from the projected visit date, is allowable for IM dosing but not preferred.** Any interruption

outside of this guidance MUST be discussed with the Medical Monitor prior to reinitiating IM IP (see Section 6.9.1).

Guidance is provided below on general participant management and IP interruptions based on the severity of the AE. Information regarding permitted substitutions \ is provided in Section 6.8. All changes in the IP regimen must be accurately recorded in the participant's eCRF.

Note: For participants receiving an ABC-containing product as part of the background regimen, in the event of a discontinuation of ABC for any reason, reinitiation of this drug should be undertaken with caution. The investigator should obtain a complete history of the events surrounding the discontinuation of the ABC-containing product, evaluate for the possibility of a clinically suspected HSR, and initiate participant management as outlined in the Local Country Prescribing Information, regardless of a participant's *HLA-B*5701* status. Screening for the presence of *HLA-B*5701* is recommended prior to reinitiating treatment with ABC-containing products in participants of unknown *HLA-B*5701* status who have previously tolerated ABC but is not required to confirm study eligibility.

7.4.3.10. Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue study drug at the discretion of the investigator. Participants who choose to withdraw from the study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Participants who develop ALT ≥3 times ULN while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA + RPV LA

7.4.3.11. Grade 3 Toxicity/Adverse Event

Participants who develop a Grade 3 AE or toxicity should be managed as follows:

- If the Investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by IP, dosing may continue after discussion with the Medical Monitor.
- Participants who develop a Grade 3 AE or toxicity, which the Investigator considers related or possibly related to the IP, should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, IP may be re-started.
- Should the same Grade 3 AE recur within 28 days in the same participant, the IP should be permanently discontinued and the participant withdrawn from study.
- Participants experiencing Grade 3 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and to have withdrawal study evaluations completed. A follow-up visit should be performed 4 weeks after the last dose of IP. Any participant receiving at least one dose of CAB LA

and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Phase for 52 weeks of follow up.

- Participants with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue IP if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 7.4.4.1). Isolated Grade 3 lipid abnormalities do not require withdrawal of IP.

7.4.3.12. Grade 4 Toxicity/Adverse Event

- Participants who develop a Grade 4 AE or toxicity must have IP permanently discontinued. However, if the Investigator has compelling evidence that the AE is not causally related to the IP, dosing may continue after discussion with, and assent from, the Medical Monitor. Participants should be rechecked each week until the AE returns to Grade 2.
- Participants experiencing Grade 4 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Phase for 52 weeks of follow up.
- Participants with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue therapy if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 7.4.4.1). An in-clinic follow-up visit will be performed approximately 4 weeks after the last dose of study medication if AEs, SAEs, or laboratory abnormalities considered potentially harmful to the participant are ongoing at the last on-study visit. Isolated Grade 4 lipid abnormalities do not require withdrawal of IP.

7.4.4. Specific Toxicities/Adverse Event Management'

General guidelines for the management of specific toxicities that are considered to be associated with treatment of HIV patients.

Participants who permanently discontinue study drug for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-up study evaluations as noted in Section 7.4.3.3.

7.4.4.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event etiology during administration of study drug and the follow-up phase. All Phase 3 participants who meet liver stopping criteria will be adjudicated by the ViiV Safety and Labelling Committee (VSLC) – resulting in a case

summary, adjudication, and management plan. The VSLC contains an external expert hepatologist, familiar with both DILI and cabotegravir, who will participate in this review. This committee meets on a 3-weekly basis, and can be convened on an ad hoc basis as needed.

7.4.4.2. Diarrhea

Participants with Grade 1 or 2 diarrhea may continue study treatment without interruption. Participants with diarrhea of any toxicity grade may be treated symptomatically with anti-motility agents; however, the recommended daily dose of the chosen anti-motility agent must not be exceeded. If symptoms persist or get worse on the recommended daily dose of the chosen anti-motility agent then the anti-motility agent must be discontinued and consultation made with the Medical Monitor.

For participants with Grade ≥3 diarrhea that is unresponsive to the recommended dose of the anti-motility agents and for which an alternative etiology (e.g., infectious diarrhea) is not established, the treatment with the anti-motility agent and IP must be interrupted until resolution of diarrhea to Grade ≤2 or Baseline, after which IP and background ART may be resumed after discussion and agreement with the Medical Monitor. If Grade ≥3 diarrhea recurs within 28 days upon the resumption of IP, the IP should be permanently discontinued and the participant withdrawn from the study. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Phase for 52 weeks of follow up.

If loperamide is used for treatment of diarrhea, local prescribing information should be followed with respect to dose and frequency of administration. Loperamide dosing should not exceed local prescribing information.

7.4.4.3. Hypertriglyceridemia/ Hypercholesterolemia

Samples for lipid measurements **must** be obtained in a fasted state according to the Time and Events table (Section 7.1). Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive IP. Clinical management of participants with hypertriglyceridemia/hypercholesterolemia should **not** be based upon non-fasting samples (obtained in the fed state). A confirmatory fasting triglyceride and/or cholesterol level should be obtained prior to the institution of medical therapy for hyperlipidemia. Isolated Grade 3 and Grade 4 lipid abnormalities do not require withdrawal of IP.

Please see the Recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group [Dube, 2003] for full discussion of management of hyperlipidemia in the context of HIV therapy.

7.4.4.4. Seizures

Three cases of seizures have occurred in the CAB program cumulatively through 01 October 2015.

ViiV Healthcare has reviewed these cases in detail and does not believe they constitute a reasonable likelihood of causation associated with CAB. This assessment is supported by the lack of preclinical signal, class effect or known CNS mechanism, the relatively low frequency of seizures relative to expected rates in both healthy and HIV positive participants and clinical confounders in each case. The Sponsor considers the risk of developing seizures on the study as being no higher than that of the rest of the HIV-1 infected population.

Seizures that occur on study should be managed according to the local guidelines on emergency seizure management which may include treatment with benzodiazepines, general supportive treatment, exclusion of metabolic and toxicological abnormalities using laboratory tests, septic workup and excluding underlying structural abnormalities with neuroimaging.

Where seizures occur, the Sponsor would like to better characterize these occurrences to enable systematic analyses.

Investigators are requested to document and report seizure or possible seizure events promptly (within 24 hours of learning of the event) to the Sponsor for evaluation and onward reporting. Data should be documented on the appropriate eCRF seizure page.

7.4.4.5. Creatine Phosphokinase (CPK) Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2-4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained.

Grade 4 elevations in CPK should have a repeat assessment after the participant has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the IP, IP should be discontinued and the participant withdrawn from the study. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART enter the Long-Term Follow-Up Phase for 52 weeks of follow-up.

7.4.4.6. Lipase Elevations and Pancreatitis

Participants with asymptomatic Grade 1 or 2 elevations in lipase may be followed closely for the development of symptoms.

Participants with asymptomatic Grade ≥3 elevations in lipase that are considered possibly or probably related to IP should have IP interrupted until serum lipase returns to Grade ≤2. The lipase assay should be repeated within 2 weeks of any Grade ≥3 result. Participants with persistence of Grade ≥3 lipase in the absence of other diagnoses or reoccurrence of lipase elevation (at Grade ≥2) following reintroduction of IP should permanently discontinue IP.

Participants with a confirmed diagnosis of clinical pancreatitis that is considered possibly or probably related to IP should have IP held. After complete resolution of the episode,

participants may be re-challenged with IP after discussion with the Medical Monitor, only if the Investigator has compelling evidence that the event was not caused by IP. Upon re-challenge, lipase determinations should be performed every 2 weeks for at least 6 weeks after re-initiation of treatment. With any elevation of lipase of Grade ≥2 or any recurrence of symptoms, the participant should discontinue IP and be withdrawn from study.

Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Phase for 52 weeks of follow up.

Drug Restart Following Transient Resolving Liver Events Not Related to Study Drug

Approval by VSLC for drug restart can be considered where:

Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension, and liver chemistries have improved to normal or are within 1.5 × baseline and ALT <3 × ULN). Ethics Committee or IRB approval of drug restart must be obtained, as required.

If restart of drug is approved by VSLC in writing, the participant must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.

The participant must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.

Study drug must be administered at the dose specified by VSLC.

Participants approved by VSLC for restarting study drug must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

Refer to Section 12.3, Appendix 3: Liver Safety – Study Treatment Restart Guidelines for further details.

7.4.4.7. Decline in Renal Function

Participants who experience an increase in serum creatinine from Baseline of 45 micromoles/liter (μMol/L) (or 0.5 milligrams/deciliter [mg/dL]) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine and urine total protein/albumin ratios should also be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

Participants who have a decline in the estimated GFR (using the CKD-EPI method) of >50% from Baseline must return for a confirmatory assessment as soon as possible

[Levey, 2009]. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios should also be done at this confirmatory visit. If the estimated GFR has declined by >50% (confirmed), then study drug should be withheld and the investigator should contact the study medical monitor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding factors (e.g., background therapy, other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained.

7.4.4.7.1. Proximal Renal Tubule Dysfunctions

PRTD is defined as:

Confirmed rise in serum creatinine of ≥0.5 mg/dL from Baseline AND serum phosphate <2.0 mg/dL;

Either of the above accompanied by any two of the following:

Glycosuria (≥250 mg/dL) in a non-diabetic;

Low serum potassium (<3 mEq/L);

Low serum bicarbonate (<19 mEq/L).

Participants meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks of diagnosis. A urinalysis should also be performed at the time of the confirmatory assessment. If PRTD is confirmed participants should have study drug withheld and the investigator should contact the Study medical monitor to discuss the rationale for restarting study drugs (if appropriate). If a participant in the current ART arm is also receiving TDF, then a dose adjustment may be considered if restarting study drug unless participants met renal toxicity stopping criteria (see Section 7.4.4.7). Consideration for confounding factors (e.g., NRTI backbone, other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If study drug is reinitiated, it should have been withheld for no more than 4 weeks.

7.4.4.8. Proteinuria

Participants with an abnormal urine microalbumin/creatinine ratio (>0.3 mg/mg, >300 mg/g, or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine microalbumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be given to additional evaluation after consultation with the study medical monitor. Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g, or >34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 µmol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If

confirmed, the study medical monitor should be contacted immediately. Agreement on further management should be agreed between the investigator and medical monitor.

7.4.4.9. QTc Prolongation

Participants with an average QTc interval > 550 msec from three or more tracings separated by at least 5 minutes should have IP discontinued. These criteria are based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period (~5-10 minutes) and use the averaged QTc values of the 3 ECGs to determine whether the participant should be discontinued from the study. If an alternative cause of the QT prolongation is determined (e.g., participant receiving drug known to cause prolonged QT or TdP), then IP may be restarted after consultation with, and agreement by, the Medical Monitor.

7.4.4.10. Injection Site Reactions (ISRs)

Injection site reactions will be managed through investigator assessment throughout the study. All ISRs that are either serious, Grade 3 or higher, or persisting beyond 2 weeks must be discussed with the Medical Monitor to determine etiology and assess appropriate continued study participation.

Digital photographs may be documented where possible on all participants who have an injection site reaction, with observable findings, that is either serious or Grade 3 or higher, or that persists beyond 2 weeks. Dermatology will be consulted on all participants who have an injection site reaction considered serious, Grade 3 or above, or if clinically significant and persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.

Details regarding photo collection and any other follow up will be given by the Medical Monitor at the time of assessment.

ISR discomfort can be managed symptomatically (e.g., cold/warm compress, acetaminophen, ibuprofen) if the reaction is interfering with the participant's ability to perform activities of daily living. The required intervention should be documented on the appropriate eCRF page.

7.4.4.11. Allergic reaction

Participants may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the study drug should permanently discontinue the CAB LA + RPV LA regimen and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE.

Participants in the current ART arm who are receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC hypersensitivity reaction (HSR) and managed appropriately as outlined in the local prescribing information for ABC.

7.4.4.12. Abacavir Hypersensitivity Reaction (ABC HSR)

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR). A detailed clinical description of this reaction (including the type and severity of events that can occur on re-challenge or reintroduction following ABC interruption for non-HSR reasons) and guidance regarding its management are included in the Local Country Prescribing Information for EPZICOM. Investigators must familiarize themselves with this information on ABC HSR in the Local Country Prescribing Information for each of these products prior to initiating participants on ABC therapy.

Studies have shown that carriage of the *HLA-B*5701* allele is associated with a significantly increased risk of a HSR to ABC. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*5701* and subsequently avoiding ABC in *HLA-B*5701* positive patients, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$). In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of participants who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively.

In any participant treated with ABC, the clinical diagnosis of suspected HSR (as detailed in the Local Country Prescribing Information) must remain the basis of clinical decision making. Regardless of *HLA-B*5701* status, it is important to permanently discontinue ABC and not re-challenge with ABC (i.e., ZIAGEN, EPZICOM/KIVEXA, TRIZIVIR, or TRIUMEQ) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

7.4.4.12.1. Essential Patient Information

With reference to Local Country Prescribing Information and the 'Participant Information and Consent Form', Investigators must ensure that participants are fully informed regarding the following information on the hypersensitivity reaction prior to commencing ABC therapy:

- Participants must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased in individuals who are *HLA-B*5701* positive.
- Participants must also be informed that *HLA-B*5701* negative individuals can also experience abacavir hypersensitivity reaction. Therefore, ANY participant who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT their doctor IMMEDIATELY.

- Participants who are hypersensitive to abacavir should be reminded that they must never take any abacavir containing medicinal products (e.g., ZIAGEN, EPZICOM, KIVEXA, TRIZIVIR, or TRIUMEQ) again, regardless of their *HLA-B*5701* status.
- In order to avoid restarting abacavir, participants who have experienced a hypersensitivity reaction should be asked to return any remaining EPZICOM / KIVEXA tablets to the Investigator or site staff.
- Participants, who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting EPZICOM / KIVEXA as more severe symptoms may recur within hours and may include life-threatening hypotension and death.
- Each participant should be reminded to read the Package Leaflet included in the EPZICOM / KIVEXA pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

7.4.4.12.2. Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH E2A, 1994 definitions of seriousness listed in Section 12.6.2 then, in addition to reporting the case as an SAE, the ABC HSR eCRF should also be completed within one week of the onset of the hypersensitivity reaction. Clinically suspected cases of HSR to ABC that do not meet criteria as an SAE can be recorded as an AE.

7.4.4.13. Rash Without ABC HSR Symptoms

Including serious skin reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme or rash with significant liver dysfunction.

Participants should be instructed to contact the Investigator as soon as possible if they develop a rash on study.

Participants who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens - Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN, and Erythema Multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, ABC (and / or all other concurrent medication(s) suspected in the Investigators causality assessment) should be discontinued, and the participant should not be re-challenged with any ABC-containing medicinal product (i.e., ZIAGEN, TRIZIVIR, EPZICOM, or KIVEXA).

As many products other than abacavir also cause rash and/or serious skin reactions, all other medicinal products that the participant is receiving should also be reviewed and discontinued as appropriate.

The following guidance is provided for clinical management of participants who experience rash alone in the absence of accompanying diagnosis of ABC HSR, systemic or allergic symptoms or signs of mucosal or target lesions.

CAB is an analogue of DTG and mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. No instances of serious skin reaction, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme, have been reported for DTG in clinical trials. For further characterization of HSR and rash observed with DTG-containing ART, please see the current version of the IB [GlaxoSmithKline Document Number RM2007/00683/09].

Rash is an adverse drug reaction (ADR) for RPV. In clinical trials, most rashes emerged during the first 4 weeks of treatment, were transient, and usually mild (Grade 1) to moderate (Grade 2). There were no Grade 4 rashes and none were serious. Treatment-related Grade 3 rash was reported in 0.1% of participants in the RPV group. Treatment-related rash led to permanent discontinuation in 0.1% of participants in the RPV group. No cases of erythema multiforme, SJS or TEN have been reported during clinical development of RPV.

Participants with an isolated Grade 1 rash may continue study drug at the Investigator's discretion. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

Participants may continue study drug for an isolated Grade 2 rash. However, study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The participant should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Participants should permanently discontinue study drug [and all other concurrent medication(s) suspected in the Investigators causality assessment] for an isolated Grade 3 or 4 rash, except where the etiology of the rash has been definitively diagnosed as NOT attributable to study drug (see below), and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE. Every effort should be made to collect as much information as possible about the evolution of the event and any relationship with potentially related medical events (e.g., viral infection) or start of concomitant medication.

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings – see Section 12.2, Appendix 2).

However, if the etiology of the rash has been definitively diagnosed as being unrelated to study drug and due to a specific medical event or a concomitant infection or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided. In this situation, the study drug should be continued.

Participants in the current ART arm who are receiving ABC as part of their regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information for ABC.

Any rash that is possibly related to study drug, and is present between Day 1 and The Week 4b visit, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA.

Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the Long-Term Follow-Up Phase for 52 weeks of follow-up.

7.4.5. Suicidal Risk Monitoring

Participants with HIV infection may occasionally present with 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 INIs. Additionally, depression and anxiety has been reported in some participants being treated with RPV. Therefore, it is appropriate to monitor and closely observe participants prospectively before and during treatment for suicidal ideation and/or behavior, or any other unusual changes in behavior. It is recommended that the Investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

Assessment of treatment-emergent suicidality will be monitored during this study using the electronic version of the Columbia Suicide-Severity Rating Scale (eC-SSRS). The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. The eC-SSRS is to be administered as a patient completed questionnaire specified in the Time and Events Table

(Section 7.1). The eC-SSRS will be conducted electronically by telephone or by computer/tablet connected to the internet.

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the Adverse Event (non-serious or Serious Adverse Events) eCRF form on any participant that experiences a possible suicidality-related adverse event while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to ViiV/GSK within one week of the investigator diagnosing a possible suicidality-related adverse event. All sites should have a plan in place for managing possible risks for suicide related events.

7.4.6. Pregnancy

7.4.6.1. Pregnancy testing

Women of childbearing potential must have a negative pregnancy test at Screening, Baseline (Day 1), and Week 56 for women transitioning into the Extension Phase from the current ART arm.(prior to administration of first CAB LA and / or RPV LA injection). Pregnancy testing will also be conducted as per the Time and Events Table (Section 7.1) and at anytime during the trial when pregnancy is suspected.

Additionally, the Medical Monitor may request that a urine pregnancy test be performed in the event of a treatment interruption greater than 7 days.

7.4.6.2. Time Period for Collecting Pregnancy Information

Pregnancy information will be collected from Day 1 until the last follow-up assessment. This includes the entirety of the Long-Term Follow-Up Phase.

Female participants that have received at least one dose of CAB LA or RPV LA and do not enter the Long-Term Follow-Up Phase should use an acceptable method of contraception (see the SPM for a listing of examples of acceptable hormonal contraception) until at least 52 weeks after the last dose of study drug. If a participant becomes pregnant within 52 weeks of the last dose of study drug the participant should notify the study site.

7.4.6.3. Action to be Taken if Pregnancy Occurs

Any individual who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study and must immediately discontinue study drug. Participants who have received at least one dose of CAB LA and/or RPV LA should discontinue further dosing and continue oral HAART in the Long-Term Follow-Up Phase (see Section 4.2.4 above), after discussion with the Medical Monitor.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure participant safety, if a pregnancy is reported then the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

Participants who have received at least one IM injection of CAB LA and RPV LA and become pregnant during the study will have additional PK samples collections to monitor CAB LA and RPV LA exposure throughout the pregnancy and at the time of delivery. Additionally, there will be an optional umbilical cord blood collection at time of delivery and/or breast milk after delivery, requiring additional parental informed consent. Cord blood and breast milk samples would be used to better understand the level of PK exposure to the neonate, if any.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as SAEs.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to ViiV/GSK.

GSK's central safety department will also forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of ARV products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

7.4.7. Physical Exams

Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems. Height and weight will also be measured and recorded as per the Time and Events Table in Section 7.1 above.
- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- The site of IM injection administration should be assessed at every visit for signs of any possible reaction. See Section 7.4.4.10 for additional information.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.8. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate. These will be recorded as per the Time and Events Table in Section 7.1.

7.4.9. Electrocardiogram (ECG)

A 12-lead ECG will be performed in a semi-supine position. On Day 1, (Baseline), ECGs should be performed in triplicate prior to first dose. At Week 4b and Week 48 of the Maintenance Phase, a 2 hour post dose ECG will be performed for participants randomized to CAB LA + RPV LA. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each participant. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations. Refer to the Time and Events Table for collection timepoints (Section 7.1). Refer to Section 5.5.2 for [QTc] withdrawal criteria and additional [QTc] readings that may be necessary

7.5. Pharmacokinetics

Plasma samples for determination of CAB and RPV concentration will be collected throughout the Maintenance and Extension Phases of the study. Additional samples will be collected for storage during the Long-Term Follow-Up Phase (blood and plasma). Samples (blood and plasma) for determination of RPV concentrations will be protected from light at all times, from sampling collection through analysis.

7.5.1. PK Sample Collection

Blood samples for evaluation of CAB (2mL each) and RPV (2mL each) plasma PK concentrations will be collected from all participants randomized to receive CAB + RPV as described in Table 8.

At Week 4b (and Week 56b for participants transitioning into the Extension Phase from the current ART arm), PK samples must be collected within the window of 20-28 hours after the last oral dose of CAB + RPV was taken the day prior to the clinic visit. Participants will take their final dose of oral CAB + RPV in the clinic at Week 4b (or Week 56b) after the pre-dose PK sample.

Participants will be expected to complete a PK dosing diary card noting the date and time of the last three oral doses of IP prior to the scheduled clinic visits at Week 4b (or Week 56b). The information from the diary card and the actual date and time of the PK samples will be recorded in the eCRF. Additionally, dosing information on the clinic day, including dosing and the actual date and time of the PK samples, must be recorded

on the eCRF. Participants will take their last dose of oral CAB + RPV in the clinic at Week 4b (or Week 56b) after the pre-dose PK sample.

PK concentrations will be summarized and used to evaluate potential exposure-response relationships.

The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Table 8 CAB and RPV Plasma Pharmacokinetic Sample Schedule

Group	Analyte	Sample Times Relative to Dose
All participants receiving CAB LA + RPV LA IM	CAB	Pre-Dose: Week 4b, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 96, and Withdrawal. 2 Hours Post Dose: Week 4b, Week 48 ,Week 96 1 Week Post Dose: Week 5 and Week 41 PK samples for storage only: Pre-dose: Week 64, 72, 80 and 88 Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
	RPV	Pre-Dose: Week 4b, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 96, and Withdrawal. 2 Hours Post Dose: Week 4b, Week 48, Week 96 (i 1 Week Post Dose: Week 5 and Week 41 PK samples for storage only: Pre-dose: Week 64, 72, 80 and 88 Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
Current ART Arm Transitioning to CAB LA + RPV LA IM following Week 48	CAB	Pre-Dose: Week 56b, Week 60, and Withdrawal 2 Hours Post Dose: Week 56b Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
	RPV	Pre-Dose: Week 56b, Week 60, and Withdrawal 2 Hours Post Dose: Week 56b Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12

PK visit window and sample collection: Pre-dose ***visits*** (from projected visit date): ±3 days (1st injection), minus 7 days (2nd and 3rd injection), and ± 7days (4th and all subsequent injections); Pre-dose sample collection at Week 4b (and Week 56b for participants transitioning from the current ART arm): 20 to 28 hours after the last oral

dose of CAB and RPV was taken; 2 hours post dose: ±one hour; one week post dose visits: 3 to 10 days post injection.

If a participant withdraws from the study a PK sample should be collected as early as practically possible (i.e., at withdrawal visit or on the day the withdrawal decision was made).

Additional details concerning handling of PK samples, labeling and shipping directions will be supplied in the central laboratory manual.

Samples for determination of RPV will be protected from light until analyzed.

7.5.2. Rationale of PK Sampling Strategy

Blood sampling for CAB and RPV concentrations will be performed during the Maintenance Phase of the study to evaluate PK in HIV infected participants. The proposed PK visits and sampling scheme at each visit presented in Section 7.1 is based on consideration of available PK data to support interim and final PK and PK/Pharmacodynamic (PD) analysis planned in this study.

7.5.3. Sample Analysis

7.5.3.1. CAB Sample Analysis

Plasma CAB analysis will be performed under the control of PTS-DMPK, GlaxoSmithKline, the details of which will be included in the Study Reference Manual (SRM). Concentrations of CAB will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for CAB any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS-DMPK, GSK protocol. No human DNA analysis will be performed on these samples.

7.5.3.2. RPV Sample Analysis

Plasma RPV analysis will be performed under the control of Janssen R&D. Concentrations of RPV will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

Once the plasma has been analyzed for RPV any remaining plasma may be used by the sponsor for further exploratory work on pharmacokinetics, metabolites, plasma protein binding, protein analysis, and biochemistry. No human DNA analysis will be performed on these samples.

7.6. Biomarker(s)

Blood and urine are being collected to perform renal, and bone assessments, as outlined in Table 6. Renal biomarkers include Cystatin C (blood), Retinol Binding Protein (RBP, blood/urine), urine albumin/creatinine ratio, urine protein/creatinine ratio, urine

phosphate and serum creatinine. Bone biomarkers (blood) include bone-specific alkaline phosphatase, procollagen type 1 N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D.

7.7. Genetics

Information regarding genetic research is included in Appendix 5: Genetic Research.

7.8. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide PBMCs and plasma for storage samples according to the Time and Events Table (see Section 7.1) for potential viral genotypic and phenotypic analyses.

Details concerning the handling, labeling and shipping of these samples will be supplied separately. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard PhenoSense and GenoSure testing methods for protease (PRO), reverse transcriptase (RT), and integrase assays.

7.8.1. HIV-1 Polymerase Viral Genotyping and Phenotyping

Participants meeting confirmed virologic failure will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from samples collected at the time of meeting suspected virologic failure; these results will be reported to the investigator as soon as available to provide guidance for election of an alternative regimen.

7.8.2. HIV-1 Exploratory Analysis

Additional analyses for HIV-1 resistance may, for example, be carried out on peripheral blood mononuclear cell (PBMC) samples collected at Baseline and/or on stored blood samples from other relevant time points. These analyses may include but are not limited to additional viral genotyping and/or phenotyping, as well as other virologic evaluations such as linkage and minority species analyses, low level HIV-1 RNA quantitation and measurement of viral replicative capacity. HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from participants who have HIV-1 RNA ≥200 c/mL regardless of confirmatory HIV-1 RNA.

7.9. Value Evidence and Outcomes

Health outcomes assessments will be conducted according to the Time and Events Table (Section 7.1). Assessments are recommended to be administered with a electronic site pad or paper instrument at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments with the exception of the NRS (administered post injection).

The 12-item Short Form Health Survey (SF-12) is a measure that describes the degree of general health status and mental health distress [Ware, 1995]. The SF-12 contains 12

items and it is derived from the Medical Outcomes Study 36-Item Short Form Health Survey.

The HIV Treatment Satisfaction Questionnaire (HIVTSQ) [Woodcock, 2001 and Woodcock, 2006] was developed to evaluate treatments for HIV and patient satisfaction. The original HIVTSQ included 10 items and underwent two stages of psychometric validation (Woodcock, 2001, Woodcock, 2006). Recently, the HIVTSQ was adapted to include injectable treatment for HIV following a qualitative study with HIV patients in five European countries. The adaptation of the HIVTSQ included two additional items related to the mode of administration (i.e., long acting intramuscular injection). These are:

- Item 11. How easy or difficult have you been finding your treatment to be recently?
- Item 12. How satisfied are you with the amount of discomfort or pain involved with your present form of treatment?

Psychometric analyses from three datasets (one from the UK, one from the USA and one from the LATTE-2 trial) reveal that the addition of two items in the original version of the HIVTSQ is suitable and does not reduce the overall validity of the questionnaire. The current study will be using the HIVTSQs (status version) and the revised HIVTSQc (change version) of this recently developed HIVTSQ 12-item questionnaire. The HIVTSQ 12-item questionnaire retains the option of calculating the total score as if it only had the original 10 items (as the original 10 items are included in the HIV-TSQ12). In addition it allows for calculation of an 11-item scale score including the "easy/difficult" item (item-11). The "pain/discomfort" item (item-12) will be included in the questionnaire as a stand-alone item to evaluate potentially painful injectables. These measures will assess change in treatment satisfaction over time (in the same participants) and compare current satisfaction with previous treatment satisfaction, from an earlier time point.

The Perception of Injection (PIN) questionnaire explores the bother of pain at the injection site and ISR, anxiety before and after injection, willingness to receive an HIV injectable treatment the following visit and satisfaction with the mode of treatment administration of individuals receiving injection and perceptions of individuals associated with receiving injections. The PIN questionnaire was derived from the Vaccines' Perception of Injection (VAPI) questionnaire (Chevat, 2009), and adapted for HIV-infected patients who will receive the CAB LA and RPV LA regimen.This measure contains 21 items that measure pain at injection site, local site reactions, impact on functioning and willingness to pursue injectable treatment outside of a clinical trial. Scores range from 1 to 5, and questions are phrased in such a way as to ensure that 1 always equated with the most favourable perception of vaccination, and 5 the most unfavourable.

The ACCEPT questionnaire is a generic medication acceptance measure assessing how patients weigh advantages and disadvantages of long-term medications (Marant, 2012). ACCEPT may be a predictor of patients' future adherence to and/or persistence with their

treatment. While the ACCEPT questionnaire consists of 25 items that capture six dimensions, we will use three questions that focus on general acceptance of study medication.

The HIV/AIDS Targeted Quality of Life (HAT-QoL) instrument [Holmes, 1998] originally contained 42 items, grouped into nine dimensions, assessing overall function and well-being. For the purposes of this study, ViiV Healthcare is using a shorter version adapted from the original version. This shorter version contains 14 items grouped into the three following dimensions: "life satisfaction", "disclosure worries" and "HIV medication". All items use a ''past 4 weeks'' timeframe and a Likert response scale from 1=''all of the time'' to 5=''none of the time''

The Numeric Rating Scale (NRS) is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of his/her post-injection pain. The NRS is anchored by 0 representing "No pain" and 10 representing "Extreme pain".

The "Reason for Switch" question will contain a single item exploring the reasons why patients choose to switch study medication. The single item will include six possible response options.

The "Preference" questions will contain a single item exploring whether patients prefer the CAB LA + RPV LA injectable treatment or the current oral ART or oral ARV regimen.

Qualitative interviews may be conducted regarding their experience with study treatment. These would be conducted under a separate IRB approved consent. Participation in the interviews would be voluntary.

7.9.1. Value Evidence and Outcomes Endpoints (Secondary)

- Change from Week 5 in Dimension scores (e.g., "Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of iNjection questionnaire (PIN).

- Proportion of participants considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the Perception of iNjection questionnaire (PIN).

- Change from baseline in total "treatment satisfaction" score, and individual item scores of the HIVTSQs at Weeks 4b, 24, 44, 96 (or Withdrawal).

- Change in treatment satisfaction over time (using the HIVTSQc) at Week 48 (or Withdrawal).

- Change from Baseline in treatment acceptance (at Weeks 8, 24, 48, 96 (or Withdrawal from the study) using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire.

- Change from Baseline in health status at Week 24, Week 48, and Week 96 (or Withdrawal) using the 12-item Short Form Survey (SF-12).

- Change from Baseline in HR QoL (using the HAT-QoL short form) at Weeks 24, 48, 96 (or Withdrawal from the study).

- Change from Week 4b in tolerability of injections (using the NRS) at Weeks 5, 40, 41, 96.

7.9.2. Value Evidence and Outcomes Endpoints (Exploratory)

- The "Reason for switch" question will be assessed at baseline and at Week 52 in patients randomized to the "Current ART" arm.

- The "Preference" question will be assessed at Week 48 (primary analysis) in patients randomized to the "CAB LA and RPV LA" arm to explore patient preference between CAB LA + RPV LA injectable regimen and current ART regimen. The question will be assessed at Week 96 (secondary analysis) in patients randomized to "Current ART" arm who decided to switch to CAB LA + RPV LA, to explore patient preference between CAB LA + RPV LA injectable regimen and "Current ART" regimen.

8. DATA MANAGEMENT

- For this study participant data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

- Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.

- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Participant initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The study is designed to demonstrate that the antiviral effect of switching to CAB LA + RPV LA (CAB) is non-inferior to continuation of current first line antiretroviral regimen (current ART) at Week 48 in HIV-1 infected ART-experienced participants. Non-inferiority in the proportion of participants with virologic failure at Week 48 (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 copies/mL) can be concluded if the upper bound of a two-sided 95% confidence interval for the difference in failure rates between the two treatment arms (CAB – current ART) is not more than 6%.

If f_{la} is the failure rate for CAB LA + RPV LA and f_c is the failure rate for current ART then the hypotheses can be written as follows:

H0: $f_{la} - f_c \geq 6\%$ H1: $f_{la} - f_c < 6\%$

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

This study will randomize approximately 285 participants per arm. Assuming the true virologic failure rate is 3% for the CAB LA + RPV LA injectable regimen and 2% for current ART arm, a non-inferiority margin of 6%, and a 2.5% one-sided significance level, this would provide approximately 97% power to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 copies/mL) at Week 48.

This sample size of 285 participants per arm will also provide at least 90% power to show non-inferiority in the proportion of participants with plasma HIV-1 RNA <50 c/mL (per FDA's snapshot algorithm) at Week 48 over a range of true response rates, on the basis of a -10% non-inferiority margin and 2.5% one-sided significance level (see Table 13). Assuming true response rates for the CAB LA + RPV LA arm and current ART arm are both 87%, the power is at least 94% to show non-inferiority for this key secondary endpoint.

In addition, the data from this study, together with data from a separate study, 201584 (FLAIR), will be combined to assess non-inferiority using a 4% non-inferiority margin. The combined sample size from both studies (570 pooled per arm) will provide 90% power, under the assumptions described above, to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL) at Week 48.

9.2.1.1. Rationale for non-inferiority margin

The selection of the non-inferiority margins in a switch study comparing regimens (rather than individual component drugs) is exclusively informed by clinical judgment (and practical considerations) since regimen efficacy over placebo will be obvious – if the regimen efficacy were no better than placebo virtually all subjects would show virologic failure. While this implies that any non-inferiority margin would be justifiable statistically, it would not be justifiable clinically to accept more than a 4 to 6 percent increase in the rate of virologic failure relative to standard-of-care regimen(s).

The non-inferiority margin of 6% is chosen in consideration of the FDA's 2015 guidance document FDA, 2015 (Human Immunodeficiency Virus-1 Infection: Development of ART Drugs for Treatment, November 2015) which is the most current regulatory guidance from either the EMA or FDA and includes specific recommendations regarding switch studies. It suggests that margins in the neighbourhood of 4% are clinically tolerable, with typical observed rates of virological failure ranging from 1 to 3%.

As this study (201585) and study 201584 are not sufficiently powered to rule out 4% virologic failure in excess, the 6% margin chosen in each study can be viewed as defining criteria for assessing the consistency acceptability of the study-specific results prior to integration of the studies in the pooled analysis. Assuming an observed control failure rate of 2%, then non-inferiority would be shown in an individual study using a 6% margin if the observed CAB LA+RPV LA failure rate was less than 5% (that is, if the observed treatment difference was less than 3 percentage points). Accordingly, if the individual studies are successful in ruling out a 6% margin, the observed results are expected to be similar and reasonable to integrate for the purposes of the primary efficacy assessment based on the pooled analysis. In addition, a virologic failure rate in this range may be clinically tolerable given the CAB LA + RPV LA regimen may offer important advantages over standard 3-drug oral regimens such as better tolerability, as well as improved adherence and treatment satisfaction in virologically suppressed subjects. Therefore, 6% is considered to be a reasonable non-inferiority margin for the individual studies, with a more stringent 4% margin applied for the pooled analysis.

9.2.1.2. Assumption for Virologic Failure Rate at Week 48 (Primary Endpoint)

9.2.1.2.1. Control Arm

The control arm will be comprised of participants whose viral load at time of randomization is suppressed (<50 c/mL) on INI-, NNRTI- or PI- based regimens. Based on these data, reasonable assumptions for the true failure rates are 2% for the control arm and 3% for the CAB + RPV LA injectable regimen.

Table 9 shows the Snapshot response and failure rates observed in five recent stable switch studies. Table 10 shows the difference in snapshot failure rates between Week 48 and Week 96 observed in recent treatment naive studies with INI-based regimens. These differences provide an approximate predication of the failure rates that may be seen in early switch studies enrolling virologically suppressed participants after 48 weeks of initial ART therapy. Taken together, these data suggest that a reasonable assumption for the true failure rate for the current ART control arm is 2%.

Table 9 Snapshot Analysis Outcomes in Recent Stable Switch Studies

Week 48			
Study	**Treatment Arm**	**HIV-1 RNA <50**	**Virologic Failure**
SPIRIT[a,b]	RPV/FTC/TDF	89%	8/317 (2.5%)
STRATEGY-PI[c]	QUAD	94%	2/290 (<1%)
	PI + FTC/TDF	87%	2/139 (1%)
STRATEGY-NNRTI[d]	QUAD	93%	3/290 (1%)
	NNRTI + FTC/TDF	88%	1/143 (<1%)
GS-292-0109[e]	E/C/F/TAF	97%	10/959 (1%)
	TDF-based regimen [f]	93%	6/477 (1%)
Week 24			
STRIIVING	DTG + ABC/3TC STR	85%	1%
	Current ART	88%	1%

a. Participants in the PI/r +2 NRTIs arm were switched to RPV/FTC/TDF at Week 24 and therefore Week 48 response data are not available.
b. [Palella, 2014]
c. [Arribas, 2014]
d. [Pozniak, 2014]
e. [Martínez, 2010]
f. E/C/F/TDF or EFC/FTC/TDF or ATV+ FTC/TDF

Table 10 Snapshot Virologic Failure Rates with INI-based Regimens in Treatment Naive Participants

Study	Regimen	Week 48	Week 96	Change
SINGLE	DTG/ABC/3TC	21/414 (5%)	42/414 (10%)	+5%
SPRING-2	DTG + ABC/3TC or TDF/FTC	20/411 (5%)	22 /411 (5%)	+0.5%
FLAMINGO	DTG + ABC/3TC or TDF/FTC	15/242 (6%)	19/242 (8%)	+2%
236-0102	E/C/F/TDF	25/348 (7.2%)	6%	-1%
236-0103	E/C/F/TDF	19/353 (5.4%)	24/353 (6.8%)	+2%
292-0104/0111	E/C/F/TAF	4%	5%	+1%
	E/C/F/TDF	4%	4%	0%

9.2.1.2.2. CAB LA + RPV LA arm

To inform the failure rate for the CAB LA + RPV LA arm, the Snapshot virologic failure rates from the Phase IIb CAB studies are displayed in Table 11 for the Intent-to-Treat Exposed population. Eligible participants included in the ITT-ME population had HIV-1 RNA <50 c/mL prior to receiving maintenance therapy at Day 1 for LATTE-2 and Week 24 for LATTE.

For LATTE, 9% (7%, excluding 1 participant classified as failure due to ART changes during the induction period) of participants previously suppressed at Week 20 to Week 24 were classified as virologic failures at Week 72 (48 weeks of maintenance treatment with oral CAB + RPV). For LATTE-2, 4% of participants randomized to CAB LA + RPV LA regimens (pooled) were classified as virologic failures after 48 weeks of maintenance treatment. Furthermore, while the failure rate was <1% at Week 48 for Q4W, there was noted variation in the snapshot failure rate over time, ranging between 0% to 3.5% through Week 48, for Q4W. These results suggests a conservative assumption for the true failure rate for the CAB LA + RPV LA Q4W arm of 3%, even

though there is no clinical rationale to suggest that the failure rate is truly higher for the CAB regimen compared to the control regimen.

Table 11 Snapshot Analysis Outcomes for Phase IIb CAB Studies (Intent-to-Treat Maintenance Exposed Population)

Week 48			
Study	**Maintenance Treatment Arm**	**HIV-1 RNA <50**	**Virologic Failure**
LATTE-2 (ITT-ME) [a]	CAB LA + RPV LA Q8W (N=115)	92%	8/115 (7%)
	CAB LA + RPV LA Q4W (N=115)	91%	1/115 (<1%)
	Oral CAB + 2NRTIs (N=56)	89%	1/56 (2%)
	Pooled LA	92%	6/230 (4%)
Week 72			
LATTE (ITT-ME) [b]	Oral CAB 30mg + RPV (n=53)	83%	9%[c]

a) Participants had HIV-1 RNA <50 c/mL at Week -4 and received oral CAB 30mg + 2 NRTIs as initial induction period therapy from Week -20 to Day 1.
b) Participants had HIV-1 RNA <50 c/mL at Week 20 and switched from oral CAB 30mg + 2 NRTIs to Oral CAB 30 mg + RPV at Week 24.
c) Includes one participant (2%) that was a virologic success but was classified as failure due to background ART change that occurred during the induction period, which is not an applicable failure category for the CAB LA + RPV LA regimen

9.2.1.3. Assumption for Response Rate at Week 48 (Secondary Endpoint)

Given the response rates shown in Table 9 and Table 11, a reasonable assumption for the true success response rate (HIV-1 RNA <50 c/mL) for both arms is 87%.

9.2.2. Sample Size Sensitivity

Figure 8 shows the sensitivity of the power curve for the primary comparison to different assumed 'true' virologic failure rates with 285 randomized per arm. Even if the failure rates were 3% for CAB LA + RPV LA and 1% for the control arm, the study will still have over 92% power to meet its primary objective.

Figure 8 Sensitivity of Estimated Power for Snapshot Virologic Failure

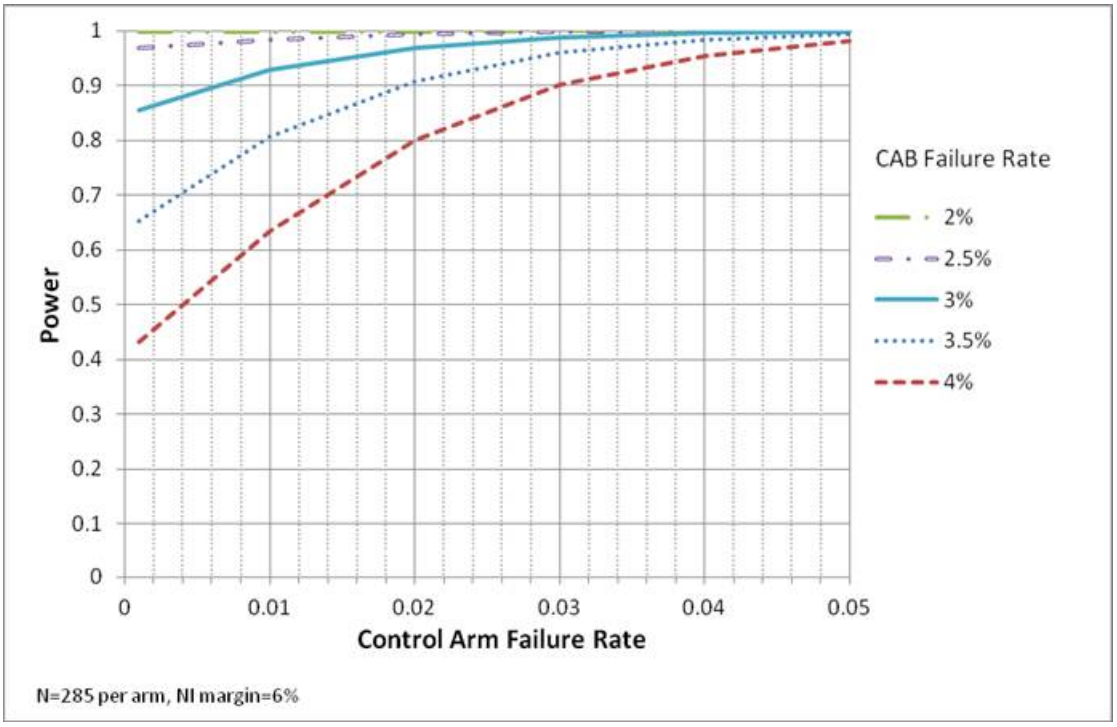


Table 12 shows the power with 285 randomized per arm and the sample size required to guarantee 90% power, for a range of 'true' virologic failure rates. For instance, even if the failure rates were 3% for CAB LA + RPV LA and 1% for the control arm, the study will still have over 92% power to meet its primary objective with the planned sample size. However, if the failure rates were 4% for CAB LA + RPV LA and 2% for control, an additional ninety-six participants per arm would be required to obtain 90% power for the primary treatment comparison.

Table 12 Sensitivity of Estimated Power for Snapshot Virologic Failure

Control Arm Virologic Failure Rate (%)	CAB LA + RPV LA Arm Virologic Failure Rate (%)	6% Non-inferiority Margin	
		Power (%) with N=285 per arm	N Required per arm for 90% Power
1%	1%	>99.9%	73
1%	2%	99.8	124
1%	3%	92.7	257
1%	4%	63.4	564
1.5%	1.5%	>99.9%	98
1.5%	3%	95.2	228
2%	2%	>99.9%	115
2%	2.5%	99.3	153
2%	**3%**	**96.8**	**205**
2%	3.5%	90.8	277
2%	4%	80.0	381
3%	3%	98.7	170
3%	4%	90.1	284

Table 13 show the sensitivity of the estimated sample size and power for the secondary endpoint comparison of response rates (HIV-1 RNA <50 c/mL at Week 48) to different assumed 'true' response rates.

Table 13 Sensitivity of Estimated Power for Snapshot Virologic Success

Control Arm Virologic Success Rate (%)	CAB LA + RPV LA Arm Virologic Success Rate (%)	-10% Non-inferiority Margin	
		Power (%) With N=285	N Required per arm for 90% Power
85%	85%	91.6	268
86%	85%	86.2	322
86%	86%	93.0	254
86%	87%	97.0	203
87%	85%	78.6	396
87%	86%	88.1	303
87%	**87%**	94.4	**238**
87%	88%	97.7	190
88%	87%	90.1	284
88%	88%	95.6	222
88%	89%	98.4	177
89%	89%	96.8	206

9.2.3. Sample Size Re-estimation or Adjustment

No sample-size re-estimation based on response data is planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

9.3.1.1. Intent-to-Treat Exposed (ITT-E)

The ITT-E population will consist of all randomly assigned participants who receive at least one dose of study drug. Participants will be assessed according to their randomized treatment, regardless of the treatment they received. The population used in the primary efficacy analysis will be the ITT-E population.

9.3.1.2. Per-Protocol Population (PP)

The Per-Protocol (PP) Population will consist of all participants in the ITT-E Population with the exception of major protocol violators. The PP will be used for sensitivity analysis of the primary endpoint.

9.3.1.3. PK Population

The PK Population will include all participants who receive CAB and / or RPVand undergo PK sampling during the study, and provide evaluable CAB and /or RPV plasma concentration data. Participants in this population will be included in the PK analysis.

9.3.1.4. Safety Population

The Safety Population will consist of all randomly assigned participants who receive at least one dose of study drug. Participants will be assessed according to actual treatment received. Unless otherwise stated, the Safety Population will be used for safety analyses.

9.3.2. Treatment Comparisons

9.3.2.1. Primary Comparison of Interest

The primary analysis will be based on the ITT-E population using the Snapshot dataset. The primary comparison of will be made at a one-sided 2.5% level of significance. Treatment with CAB LA + RPV LA will be declared non-inferior to current ART if the upper end of a two-sided 95% confidence interval for the difference between the two groups (CAB – current ART) in virologic failure rates at Week 48 lies below 6%.

9.3.2.2. Other Comparisons of Interest

The analysis described above will also be performed using the PP population and the results will be compared for consistency with the results from the ITT-E population.

9.3.2.3. Secondary comparisons

The following key secondary comparison will be tested:

- Treatment with CAB LA + RPV LA will be declared non-inferior to current ART if the lower end of a two-sided 95% confidence interval for the difference between the two groups in response rates at Week 48 lies above -10%.

- Superiority of CAB LA + RPV LA compared to continuation of current ART with respect to change from baseline HIVTSQs total score at Week 44;

- Changes in the PIN acceptance score within the CAB LA + RPV LA arm from Day 4 to Week 48

9.3.2.4. Planned Analyses

At least two analyses will be conducted to evaluate primary and secondary objectives of the protocol, one after all subjects have completed their visits at Week 48 and one after Week 96. Further data cuts and analyses may be conducted as necessary after Week 96 in order to support regulatory submissions and publications. The Week 48 analysis will be primary. No adjustment for multiplicity caused by repeated evaluation of the primary endpoint will be made as the Week 96 analyses will be secondary.

An IDMC will be instituted to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of subjects and to protect the scientific validity of this study (201585) and study 201584. An ad-hoc review of data by the IDMC will be triggered whenever the number of confirmed virologic failures (Section 5.5.4) in the CAB LA + RPV LA exceeds thresholds pre-specified in the IDMC charter. Further, an interim futility analysis will be performed for the IDMC to evaluate the efficacy and safety of CAB LA + RPV LA when approximately 50% of subjects have completed their visit at Week 24; the sponsor will remain blinded to this analysis. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

Since the statistical stopping guidelines will not result in early stopping for positive efficacy findings, these planned analyses will not inflate the type I error rate for the primary treatment comparison at Week 48.

9.4. Key Elements of Analysis Plan

The study design is open-label. However, the central GSK team responsible for the conduct and analysis of the study will not review any summaries of data grouped by treatment prior to database freeze for the primary Week 48 analysis.

This study is conducted in parallel with study 201584 (FLAIR) with the aim to pool data generated from the current study with study 201584, in order to evaluate key program objectives.

9.4.1. Primary Analyses

For the primary efficacy analysis, each participant's response (e.g., virologic failure) will be calculated according to the FDA's Snapshot algorithm. The primary analysis at Week 48 will take place after the last participant has had their Week 48 viral load assessed, including a retest if required. This algorithm treats all participants without HIV RNA data at the visit of interest (due to missing data or discontinuation of study drug prior to visit window) as non-responders, as well as subjects who switch their concomitant ART prior to the visit of interest since no switches are allowed in this protocol. Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the participant is on-treatment within the window of the visit of interest. Full details on the Snapshot algorithm will be contained in the RAP.

The primary analysis will be based on the ITT-E population using the Snapshot dataset. The primary comparison of will be made at a one-sided 2.5% level of significance. Treatment with CAB LA + RPV LA will be declared non-inferior to current ART if the upper end of a two-sided 95% confidence interval for the difference between the two groups (CAB – current ART) in virologic failure rates at Week 48 lies below 6%.

For the primary comparison, adjusted estimates of the difference in the rate of failures between the two arms will be presented along with CIs based on a stratified analysis using Cochran-Mantel Haenszel (CMH) weights. All CIs will be two-sided and the analysis will be stratified according to the baseline third agent class (INI, NNRTI, or PI) and gender at birth. If the adjusted treatment difference is not estimable due to overly sparse stratification and/or low number of subjects with virologic failure, then the primary comparison will be adjusted for baseline third agent class only; if this also encounters numerical issues then the primary comparison will be based on the unadjusted analysis.

The CMH estimate of the common difference in rates across strata will be calculated as the weighted average of the strata-specific estimates of the difference in response rates between the two arms as follows:

- If n_k is the number of CAB treated participants, m_k is the number of current ART control arm treated participants, and $N_k = n_k + m_k$ is the total number of participants in the *k*th stratum, then the CMH estimate is given by

$$\hat{d}_{cmh} = \frac{\sum W_k \hat{d}_k}{\sum W_k}$$

where

$$W_k = \frac{n_k m_k}{N_k}$$

are CMH weights and $\hat{d}_k$ are estimates of the differences in response rates between the two treatment arms, f_{la}-f_c, for the *k*th stratum.

using the variance estimator $\hat{\text{var}}(\hat{d}_{cmh})$, given by [Sato, 1989], which is consistent in both sparse data and large strata. The full equation for this variance estimate will be provided in the RAP.

The weighted least squares chi-squared statistic [Fleiss, 1981] will be used to test for one-way homogeneity across the levels of each categorical variable, with each categorical variable considered separately. Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any strata for which the stratum-specific rate estimates of either f_{la} or f_c are zero or one, and tests will be one-sided. Any heterogeneity found to be statistically significant will be explored and if necessary results will be reported for each level of the categorical variable. Investigation of heterogeneity will be confined to the primary endpoint using the Week 48 Snapshot analysis. Tests of homogeneity will be assessed at the one-sided 10% level of significance. Full details will be contained in the RAP.

On-treatment data collected from extra visits within a window will be included in the derivation of the Snapshot response/failure but summary tables using observed case (OC) datasets will only use the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows will be included in the RAP. Any changes to the original analysis plan in the protocol will be described in the RAP and/or clinical study report (CSR).

The analysis described above will also be performed using the PP population and the results will be compared for consistency with the results from the ITT-E population.

9.4.2. Secondary Analyses

A key secondary analysis will evaluate the proportion of responders (HIV-1 RNA <50 c/mL per Snapshot) at Week 48 using a Cochran-Mantel Haenszel test stratified by baseline third agent class (INI, NNRTI, or PI) and gender at birth. A non-inferiority margin of -10% will be used for this secondary comparison, where if the lower limit of the 95% confidence interval (CI) of the difference in responder rate between the two study arms is greater than -10%, non-inferiority will be demonstrated.

Proportion of participants with plasma HIV-1 RNA <200 c/mL and <50 c/mL and confirmed virologic failure, respectively, for the ITT-E population over time will be summarized using the Snapshot algorithm. Proportion of participants with confirmed virologic failures will also be summarized over time.

Absolute values and change from Baseline in plasma HIV-1 RNA and CD4+ lymphocyte count will be summarized over time.

The incidence of HIV-1 disease progression (AIDS and death) will be presented.

An efficacy analysis at Week 48 will also be presented by baseline third agent class.

The OC dataset will be the primary dataset used for analysis of safety endpoints.

Statistical analysis of selected biomarkers and fasting lipids may be performed overall and by baseline third agent class using appropriate methods for missing data. Further details will be detailed in the RAP.

The proportion of participants reporting AEs will be tabulated for each treatment group. The following summaries of AEs will be provided:

- Incidence and severity of all AEs
- Incidence and severity of treatment related AEs
- Incidence and severity of AEs leading to withdrawal
- Incidence of SAEs

The incidence and severity of treatment related AEs, SAEs and AEs leading to withdrawal will also be assessed by baseline third agent class.

Changes from baseline in laboratory (including fasting lipids) and vital signs data will be summarized by visit and treatment group. In addition, the number and percentage of participants with graded laboratory toxicities (based on DAIDS categories) will be summarized by treatment group. The number and percentage of participants with graded laboratory toxicities and the change from baseline in fasting lipids will also be assessed by baseline third agent class.

Change from baseline in renal, bone and cardiovascular biomarkers will be summarized by treatment and visit.

Further details of safety and exploratory analyses will be included in the RAP.

9.4.3. Pharmacokinetic Analyses

The GSK Division of Clinical Pharmacology Modelling and Simulation (CPMS) will be responsible for the PK analysis of CAB. The Divisions of Clinical Pharmacology and Model-Based Drug Development at Janssen Research and Development will be responsible for conduct or oversight of the PK analysis for RPV.

Actual sampling and dosing times as recorded in the eCRF will be used for analysis.

Plasma CAB and RPV concentration data will be listed and summarized by week, day, and planned sampling time in both tabular and graphical forms. A composite predose (C0) concentration may be estimated for purposes of PK/PD analysis. Post hoc estimates of PK parameters will be determined by population PK modeling separately (see Population PK Analysis below).

9.4.4. Population PK Analysis:

CAB and RPV population PK models will be constructed separately and individual Bayesian PK parameter estimates may be obtained, if the quality of the data permits. Data from this study may be merged with previous data to support the model building

process. Sources of variability in pharmacokinetic parameters will be investigated during population modeling. Demographic parameters including, but not limited to age, gender, ethnic origin, body size (weight, height, body surface area, body mass index), and relevant laboratory parameters will be evaluated as potential predictors of inter- and intra-participant variability for pharmacokinetic parameters. Population pharmacokinetic modeling will be performed using the non-linear mixed effects software NONMEM (ICON; Hanover, MD). Further details of population pharmacokinetic analyses will be described in a separate RAP. Population PK analyses will be done under separate Population-PK Reporting and Analysis Plans, and post hoc PK parameters may be determined.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between various plasma CAB and/or RPV PK parameters and pharmacodynamic measures (e.g., HIV-1 RNA, or safety measures) may be explored using simple correlation analyses or population-based PK/PD approach. Additional factors that may be considered include; e.g., age, weight, BMI, gender, race, Baseline HIV-1 RNA, HIV risk factors, CDC classification, and CD4+ cell count.

Exploratory analyses will be performed to examine the relationship(s) between plasma concentrations of CAB and RPV and pharmacodynamic endpoints. A population pharmacokinetic/pharmacodynamic modeling approach may be further applied to model the data using the nonlinear mixed effect modeling software, NONMEM (ICON LLC, Hanover, MD). Details of the PK/PD analyses plans for CAB and / or RPV will be provided in separate RAPs.

9.4.6. Viral Genotyping/Phenotyping Analyses

The incidence of treatment emergent genotypic and phenotypic resistance to NRTIs and INIs, PIs, and NNRTIs and in particular to current antiretroviral regimen and to CAB or RPV will be summarized by treatment arm for subjects meeting confirmed virologic failure criteria (Section 5.5.4). This endpoint will also be assessed by baseline third agent class. Details of the analyses to be performed will be specified in the reporting and analysis plan (RAP).

9.4.7. Health Outcomes Analyses

Statistical analysis of the key secondary comparisons (Section 7.9.1) for the change from baseline in HIVTSQs total score at Week 44 (between treatment group comparison) and within treatment group change in PIN acceptance score for subjects randomized to CAB LA + RPV LA will be performed using appropriate methods for missing data.

Further details of the analyses to be performed will be specified in the reporting and analysis plan (RAP).

9.4.8. Genetic Analyses

See Appendix 5 for details about the Genetics Analysis Plan.

9.4.9. Other Analyses

The proportion of participants with virologic failure (FDA Snapshot algorithm) and HIV-1 RNA <50 c/mL (FDA snapshot algorithm), respectively, over time through Week 48 will be analysed by important demographic and baseline characteristic subgroups factors (e.g. age, gender, BMI, race, HIV-1 subtype, and Baseline CD4+ cell counts). Changes from baseline in CD4+ lymphocyte count at Week 48 will also be summarized by subgroups. Additional details on subgroup analyses will be provide in the RAP.

Longer term antiviral and immunological effect, safety and tolerability of CAB LA + RPV LA will be assessed through Week 96 for the CAB LA + RPV LA arm (48 weeks of comparative data and 48 weeks of extension data). Antiviral and immunological effect, safety and tolerability of CAB LA + RPV LA will also be evaluated for participants switching to CAB LA + RPV LA in the Extension Phase.

Further details of exploratory analyses will be presented in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of participants begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, ViiV/GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable participant privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Investigator reporting requirements (e.g., reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- ViiV/GSK will provide full details of the above procedures, either verbally, in writing, or both.

- Signed informed consent must be obtained for each participant prior to participation in the study (see Inclusion Crietria, Section 5.1; Informed consent).
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.
- Measures and documentation towards quality assurance that will be completed prior to study initiation will also include but not be limited to the study monitoring

plan, study risk register, quality assurance plan, protocol deviation management plan, medical monitoring plan, and site feasibility assessments.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator

must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

10.8. Review Committees

10.8.1. Independent Data Monitoring Committee

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in Section 9.3.2.4 and the IDMC the charter, which is available upon request.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
ABC/DTG/3TC	Abacavir/dolutegravir/lamivudine, TRIUMEQ
ACCEPT	General acceptance" dimension of the Chronic Treatment Acceptance
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core Antibody
Anti-HBsAg	Antibodies against Hepatitis B surface Antigen
APAP	N-acetyl-para-aminophenol
ARV	Antiretroviral
ART	Antiretroviral therapy
ATV	Atazanavir
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-τ)	Area under the concentration curve from 0 hours to the time of next dosing
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAB	Cabotegravir
CAB LA	Cabotegravir long-acting
c/mL	Copies/millilitre
cART	Combination antiretroviral therapy
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CDC	Centers for Disease Control and Prevention
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
CMH	Cochran-Mantel Haenszel
CSR	Clinical Study Report
C-SSRS	Columbia Suicidality Severity Rating Scale
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
CSR	Clinical Study Report

CV	Cardiovascular
CVF	Confirmed Virologic Failure
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DRE	Disease-Related Events
DRV	Darunavir
DTG	Dolutegravir, TIVICAY
ECG	Electrocardiogram
eC-SSRS	Columbia Suicide Severity Rating Scale
eCRF	Electronic case report form
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
ETR	Etravirine
eGFR	Estimated glomerular filtration rate
EVG	Elvitegravir
FC	Fold Change
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSFV	First participant first visit
FTC	Emtricitabine
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
HbsAg	Hepatitis B surface Antigen
HAT-QoL	HIV/AIDS-targeted quality of life
HBV	Hepatitis B virus
HCG	human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HIV TSQ	HIV treatment satisfaction questionnaire
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IM	Intramuscular

INI	Integrase inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IRT	Interactive response technology
LA	Long acting
LDL	Low density lipoprotein
Lp-PLA2	Lipoprotein-associated phospholipase A2
LPV	Lopinavir
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram per deciliter
MSD=F	Missing, switch, or discontinuation equals failure
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OCT-2	Organic cation transporter
PI	Protease inhibitor
PK	Pharmacokinetic
PP	Per-protocol
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSRAE	Possible suicidality-related adverse event
QTc	Corrected QT interval
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RBP	Retinol Binding Protein
RNA	Ribonucleic acid
RPR	Rapid plasma regain
RPV	Rilpivirine, Edurant®
RPV LA	Rilpivirine long-acting
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
SPM	Study Procedures Manual
STR	Single tablet regimen
SVW	Suspected Virologic Withdrawal
TDF	Tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
TMC278	Tibotec Medicinal Compound 278

TSQ	Treatment Satisfaction Questionnaire
ULN	Upper limit of normal
US	United States
VSLC	ViiV Safety and Labeling Committee
WBC	White blood cell

Trademark Information

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM/KIVEXA
TIVICAY
TRIUMEQ
ZIAGEN

Trademarks not owned by ViiV Healthcare
Edurant
Genosure
Monogram Biosciences
PhenoSense

12.2. Appendix 2: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, November 2014

VERSION 2.0, November 2014

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilised for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-
≥ 18 years of age				hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-
Report only one				
> 16 years of age				
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV Block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

1. Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
2. As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens- Johnson syndrome OR Toxic epidermal necrolysis

3. For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND	Obvious on visual inspection AND Causing greater than minimal interference with	Disfiguring changes	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
	Causing no or minimal interference with usual social & functional activities	usual social & functional activities		
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

4. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention	Radiologic, endoscopic, or operative	Life-threatening consequences (e.g., sepsis,

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
		indicated	intervention indicated	perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis **Report only one and specify location**	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization	Life-threatening consequences (e.g., circulatory failure,

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
			indicated	hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or	Muscle pain causing greater	Muscle pain causing	Disabling muscle pain causing inability to

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
	minimal interference with usual social & functional activities	than minimal interference with usual social & functional activities	inability to perform usual social & functional activities	perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

6. BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see	Changes causing no or minimal interference with	Mild lethargy or somnolence causing greater	Confusion, memory impairment,	Delirium OR Obtundation OR Coma

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive, Behavioral, or Attentional Disturbance below)	usual social & functional activities	than minimal interference with usual social & functional activities	lethargy, or somnolence causing inability to perform usual social & functional activities	
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full- time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) **Specify type, if applicable**	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) **Specify type, if applicable**	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures **New Onset Seizure** **≥ 18 years of age**	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre- existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

7. Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
8. Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no	Thoughts of killing oneself with partial or complete plans	Suicide attempted

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
		specific plan or intent	but no attempt to do so OR Hospitalization indicated	

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
				hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan- uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Serum Sickness [11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[12] *> 5 to 19 years of age*	NA	WHO BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	NA	WHO Weight-for- height z-score < -2 to ≤ -3	WHO Weight-for-height z-	WHO Weight-for-height z-score < -3 with life- threatening
< 2 years of age	NA	WHO Weight-for- length z-score < -2 to ≤ -3	WHO Weight-for-length z-	WHO Weight-for-length z-score < -3 with life- threatening
Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

9. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10. For pain associated with injections or infusions, see the Site Reactions to Injections and Infusions section.
11. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12. WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en / for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal	Obstruction causing life- threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours	Generalized itching causing inability to perform usual social & functional activities	NA

13. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin *Direct Bilirubin[14], High* *> 28 days of age*	NA	NA	> ULN	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Calcium, High (mg/dL; *mmol/L*)				
≥ 7 days of age	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL*; mmol/L)*	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL*; mmol/L)*				

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≥ 7 days of age	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 1.53 to < 1.75	< 6.1 < 1.53
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low *(mg/dL; mmol/L)*	< LLN to 4.0 < LLN to 1.0	3.6 to < 4.0 0.9 to < 1.0	3.2 to < 3.6 0.8 to < 0.9	< 3.2 < 0.8
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance 15 or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from baseline or dialysis needed
Glucose (mg/dL*; mmol/L)*				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Glucose, Low (mg/dL*; mmol/L)*				
≥ 1 month of age	55 to 64 *3.05 to 3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life- threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL*; mmol/L)*				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 4.40 to < 5.15	200 to < 300 5.15 to < 7.77	≥ 300 ≥ 7.77	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[16], Low (mEq/L*; mmol/L)*	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL*; mmol/L)*				
> 14 years of age	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L*; mmol/L)*	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L*; mmol/L)*	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L*; mmol/L)*	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L*; mmol/L)*	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL*; mmol/L)*	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

14. Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.
15. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
16. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114 .				

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemoglobin[17]**, Low** (g/dL; *mmol/L*)[18] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
WBC, Decreased (cells/mm^3*; cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*
17. Male and female sex are defined as sex at birth. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.				

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Reference

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014]. Available from: http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf (accessed 10 September 2015).

12.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

VSLC GUIDELINES FOR DRUG RESTART OR RECHALLENGE AFTER STOP FOR LIVER CRITERIA

Drug Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI (see Drug Rechallenge Background below) this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favorable (Table 14, Figure 9).

Drug Restart refers to resuming study treatment following liver events meeting stopping criteria **in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis)**. Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury. (Table 15; Figure 10).

As this determination can be difficult, for the purpose of these guidelines, cases should be treated as rechallenges if there is any reasonable likelihood that the liver event is related to study drug. Restarts should be limited to cases in which there is clear evidence that the underlying cause of the liver event is not related to study drug.

DRUG RECHALLENGE

Background: Following drug-induced liver injury, drug rechallenge is associated with a 13% mortality across all drugs in prospective studies [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- participant currently exhibits severe liver injury defined by: ALT≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- evidence of drug-related nonclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

VSLC Decision Process for Drug Rechallenge Approval or Disapproval

- Principal Investigator (PI) requests consideration of drug rechallenge for a participant receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting participant stopping criteria in relation to DILI, with no alternative treatment
- By definition treatment naïve participants will only be considered for rechallenge if they were infected with a multi-resistant virus.
- Medical Monitor and Global Clinical Safety and Pharmacovigilance (GCSP) Physician review the participant's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and complete checklist (Table 14).
- The local operating company (LOC) medical directors (ViiV and/or GSK where applicable) should be informed that study drug rechallenge is under consideration and of the final decision, whether or not to proceed.
- The Medical Monitor and GCSP Physician are accountable to review and agree on the following prior to preparing request for rechallenge documentation for presentation to VSLC:
  - Compelling benefit of the investigational product (IP) for this participant and no alternative therapy

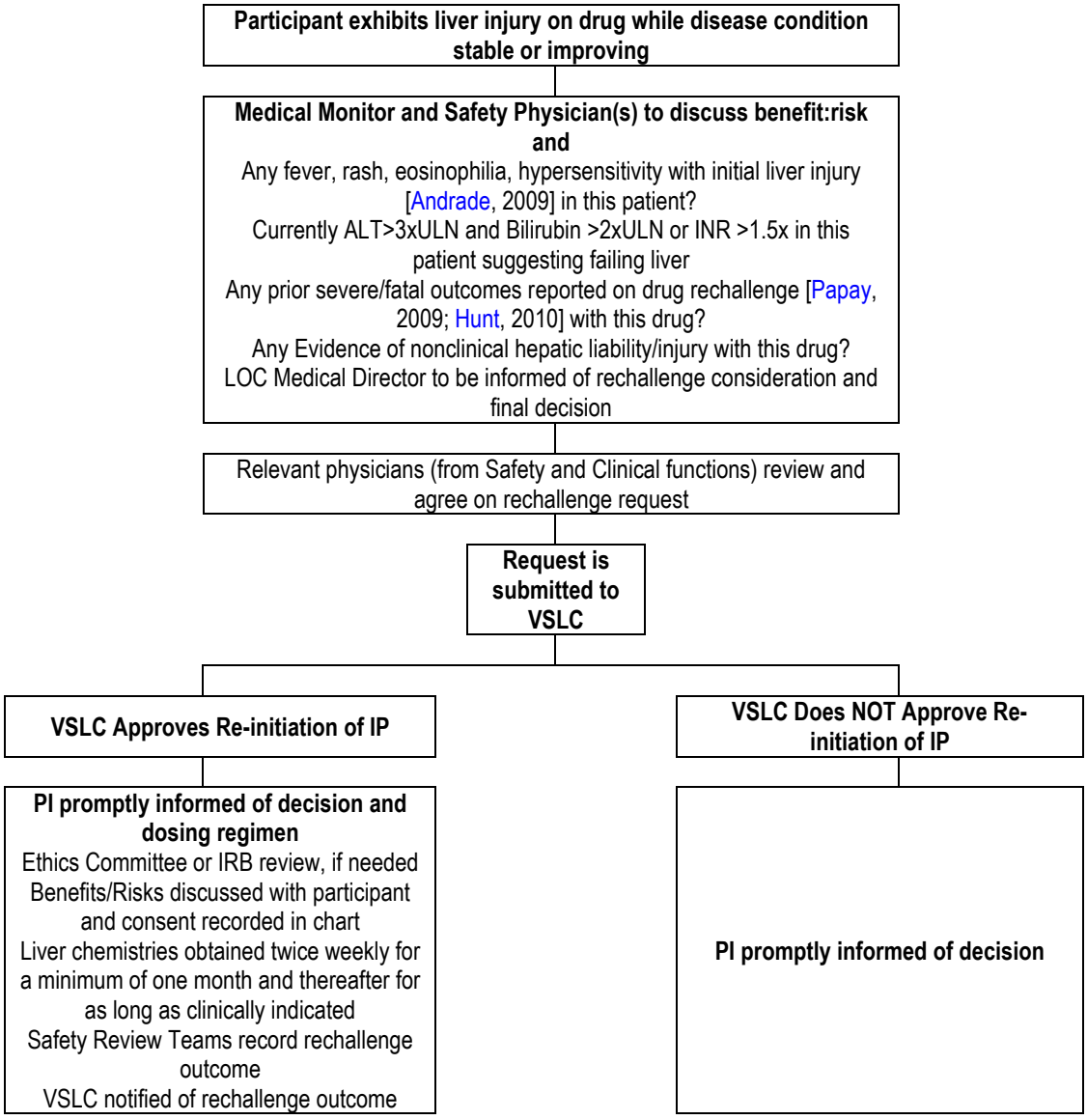
- ***must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history***

- Relative benefit-risk of drug rechallenge, with consideration of the following high risk factors:
  - Initial liver injury event included: fever, rash, eosinophilia, or bilirubin ≥2xULN (or direct bilirubin >35% of total, if available)
  - Participant currently exhibits severe liver injury defined by: ALT >3xULN, bilirubin >2xULN (direct bilirubin >35% of total, if available), or INR>1.5
  - SAE or fatality has earlier been observed with IP rechallenge
  - IP is associated with known nonclinical hepatic liability/ injury
- Relevant physicians (listed below) must review and agree on action to be taken regarding request for drug rechallenge:
  - Safety Review Team Leader, Safety Development Leader, or Senior Safety Physician
  - Medicines Development Leader (MDL) and Project Physician Leader (PPL)
- Request is taken to full VSLC for final decision

Table 14 Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)

	Yes	No
Compelling benefit of IP for this participant and no alternative therapy. **Provide brief explanation**:		
Relative benefit-risk favorable for drug rechallenge, after considering the **following high risk factors**:		
Initial liver injury event included:		
fever, rash, eosinophilia, or hypersensitivity		
bilirubin≥2xULN (direct bilirubin >35% of total)		
Participant currently exhibits ALT >3xULN, bilirubin >2xULN (direct bilirubin >35% of total, if available), or INR>1.5		
SAE or fatality has earlier been observed with IP rechallenge If yes, please provide brief explanation:		
IP associated with known nonclinical hepatic liability/ injury		
Source data defining the patients current resistance profile		
Previous drug history		

Figure 9 VSLC process for drug rechallenge approval or disapproval



DRUG RESTART

"Drug restart" can be approved by the VSLC for **transient, defined non-drug-induced** liver injury if no evidence of:

- immunoallergic injury /HLA association with injury
- alcoholic hepatitis

Study drug must be held while labs and evaluation are completed to assess diagnosis.

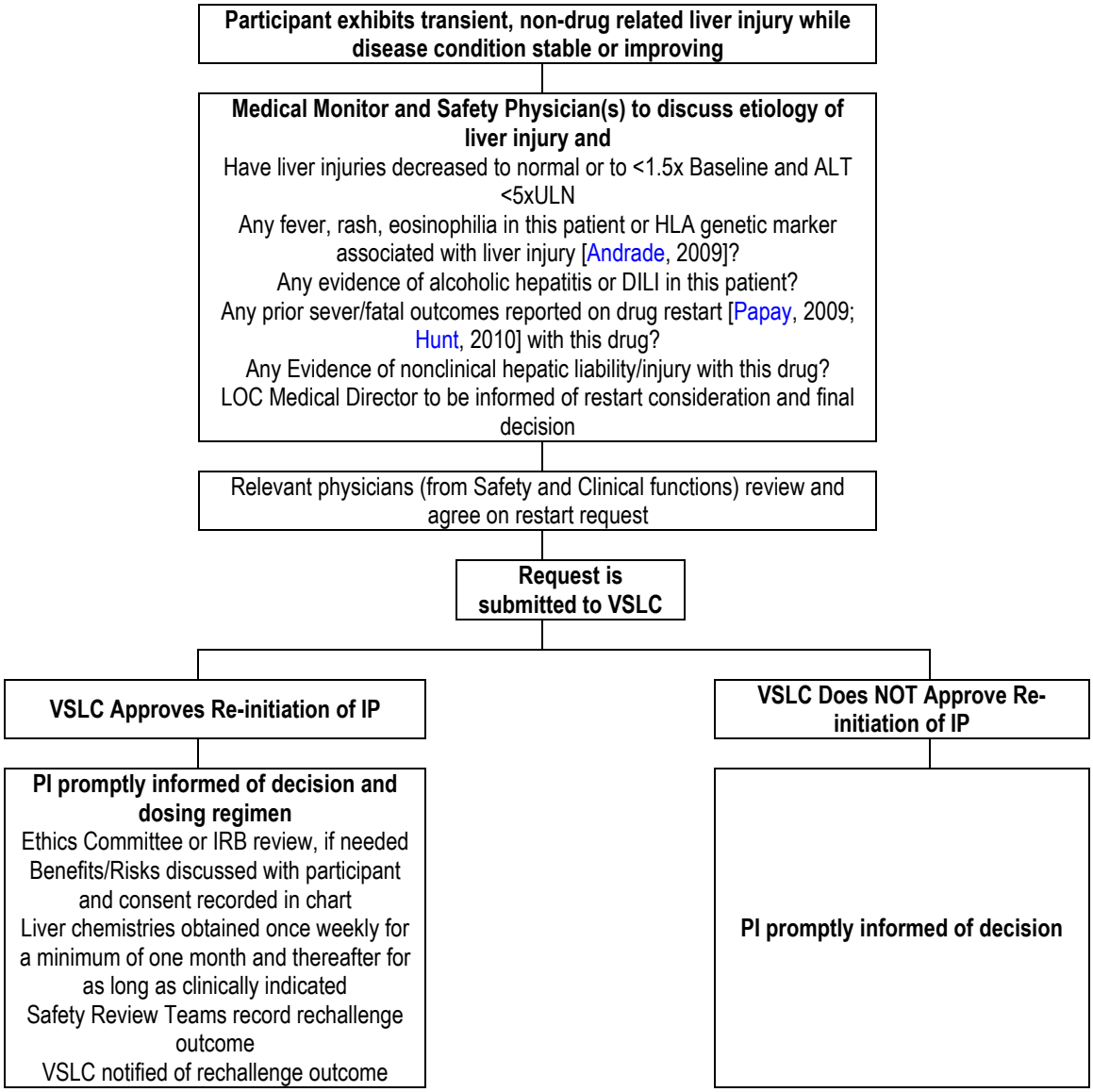
VSLC Decision Process for Drug Restart Approval or Disapproval

- Principal Investigator (PI) requests consideration of drug re-initiation for a participant stable or improving on IP, who exhibits liver chemistry elevation meeting participant stopping criteria, which is transient, non-drug-related, and liver chemistries have improved to normal or are within 1.5x baseline and ALT< 5xULN.
- GSK Medical Monitor and GCSP Physician to review the participant's diagnosis restart risk factors (Hepatotoxicity Panel consultation is available) and complete checklist (Table 15).
  - ***must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history***.
- The local operating company (LOC) medical director should be informed that study drug restart is under consideration and of the final decision, whether or not to proceed.
- Relevant physicians (listed below) must review and agree on action to be taken regarding request for drug restart:
- Safety ReviewTeam Leader, Safety Development Leader, or Senior Safety Physician
- MDL and PPL
- Request is taken to VSLC for final decision

Table 15 Checklist for Phase III drug restart after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, congestive heart failure (CHF), acute viral hepatitis), and improvement of liver chemistry to normal or ≤1.5x baseline & ALT<5xULN

	Yes	No
Is participant stable or improving on IP?		
Do not restart if the **following risk factors at initial liver injury**:		
fever, rash, eosinophilia, or hypersensitivity		
drug-induced liver injury		
alcoholic hepatitis (AST>ALT, typically <10xULN)		
IP has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		
Source data defining the patients current resistance profile		
Previous drug history		

Figure 10 VSLC process for drug restart approval or disapproval



Medical monitor, GCSP Physician and PI actions for Restart or Rechallenge following VSLC decision

Medical Monitor and GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's rechallenge (or restart) decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.
- The Safety Review Team must record rechallenge (or restart) outcomes and the GCSP Physician must send these to the VSLC (see template below).
- All severe reactions (rechallenge associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities which occur following a drug rechallenge (or restart) must be immediately reported to Line Management including, VSLC Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

PI Actions:

- The PI must obtain Ethics Committee or Institutional Review Board approval of drug rechallenge or restart, as required.
- If VSLC approves drug rechallenge or restart, the patient must sign a new informed consent containing a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
- ***Targeted drug rechallenge or drug restart consent form must be used.***
- The patient's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed ***twice weekly for 'rechallenge' cases*** and ***once weekly for 'restart' cases*** for a minimum of one month and thereafter for as long as clinically indicated following drug re-initiation. If participant exhibits protocol-defined liver chemistry elevations, IP should be discontinued as protocol specified.
- Medical Monitor and the Ethics Committee or Institutional Review Board must be informed of the patient's outcome following drug rechallenge or restart.

Drug Rechallenge or Drug Restart Outcomes Table Template

To be completed/updated and provided to VSLC with each event recorded across studies and indications

Drug Rechallenge/Restart Outcomes Table – Update with each event

Protocol#	Participant#	Rechallenge or Restart?	Safety outcome*	Drug benefit

Rechallenge/restart safety outcomes:

0 = no liver chemistry elevation

1 = recurrent liver chemistry elevation not meeting participant stopping criteria

2 = recurrent liver chemistry elevation meeting participant stopping criteria

3 = serious adverse event

4 = fatality

12.4. Appendix 4: CDC Classification for HIV-1 Infection (2014)

Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte should only be considered if the count is missing.

HIV infection, stage 0

Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

HIV infection, stage 1

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of ≥500 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

HIV infection, stage 2

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

HIV infection, stage 3 (AIDS)

- Laboratory confirmation of HIV infection, and
    - CD4+ T-lymphocyte count of <200 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or
    - Documentation of an AIDS-defining condition (see below).

Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

HIV infection, stage unknown

- Laboratory confirmation of HIV infection, and
    - No information on CD4+ T-lymphocyte count or percentage, and
    - No information on presence of AIDS-defining conditions.

Stage-3-defining opportunistic illnesses in HIV infection

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of oesophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary

- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or oesophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV.

Reference

CDC. Revised Surveillance Case Definition for HIV Infection – United States, 2014. MMWR 2014; 63 (RR-03);1-10.

12.5. Appendix 5: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate a relationship between genetic variants and:

- Response to medicine, including CAB + RPV or any concomitant medicines;
- HIV-1 susceptibility, severity and progression and related conditions.

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a RAP prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any participant who is enrolled in the clinical study can participate in genetic research. Any participant who has received an allogeneic bone marrow transplant must be excluded from genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no a priori hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the participant has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to

the participant by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last participant completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Participants can request their sample to be destroyed at any time.

Informed Consent

Participants who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Participant Withdrawal from Study

If a participant who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the participant will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample.

If a participant withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by ViiV/GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a participant withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the participant does not meet the entry criteria for participation in the study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent

and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Participant's Genetic Data

ViiV/GSK may summarize the genetic research results in the CSR, or separately, and may publish the results in scientific journals.

ViiV/GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.6.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.6.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.6.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the eCRF • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Participant-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by

the scale's developer.

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.6.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**

- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.6.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail • Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.7. Appendix 7: Pregnancy Information

12.7.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

The list does not apply to FRP with same sex partners or for participants who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- Male partner sterilisation with documentation of azoospermia prior to the female participant's entry into the study, and this male is the sole partner for that participant [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of participant's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what consistent and correct use is. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

References:

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. ICH M3 (R2). 2009.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. ICH S6 and Addendum ICH S6 (R1) 2011.

12.7.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK within 24 hours. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE within 24 hours of awareness.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in this section. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any individual participant who becomes pregnant while participating will discontinue study medication and be withdrawn from the study. If the female participant is receiving CAB LA + RPV LA, they will be followed for 52 weeks in the Long-Term Follow-Up Phase.

12.7.3. Study Duration

In this study, the Extension Phase is intended to provide access to CAB LA + RPV LA until CAB LA + RPV LA receives local (by country) Regulatory approval, and becomes commercially available. Therefore, the duration of the Extension Phase will vary from country to country and is dependent on the recruitment time for the study and the time taken to achieve local approval for marketing. During this time, participants will be monitored every 4 weeks to ensure they continue to derive clinical benefit from CAB LA + RPV LA.

12.8. Appendix 8: Country Specific Requirements

12.8.1. South Korea Investigational Product Labels

In this study subject identification number and visit number will not be included in the IP label. However, it will be tracked at site pharmacy when the IP is dispensed to each subject. (Note: This is an open label study, thus treatment number is not applicable.)

Page(s) removed - non-English text removed.

12.9. Appendix 9: Protocol Changes

12.9.1. Summary of Changes in Protocol Amendment 01 and Rationale

- Changes were made to the protocol text in the following sections to reflect revisions to the age inclusion criteria and addition of South Korea investigational product labels.

  Section 5.1 Inclusion Criteria #1
  Appendix 8 Country Specific Requirements

- Revisions were made to the protocol text to correct errors and improve accuracy of the text in:

  Section 4.2.3.2 Participants Entering from the current ART ARM
  Section 4.6.1 Risk Assessment
  Section 5.2 Exclusion Criteria #32
  Section 5.5.5.1 HIV-1 RNA Blips
  Section 6.13.2 Prohibited Medications and Non-Drug Therapies
  Section 7.1 Time and Events Table
  Section 7.3.3 HIV Associated Conditions
  Section 7.4.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs
  Section 7.4.10 Suicidal Risk Monitoring

List of Changes

Section 4.2.3.2 Participants Entering from the current ART ARM

Previously read:

The retest should be scheduled as soon as possible (but no later than 4 weeks from the Week ~~48~~ visit).

Now reads:

The retest should be scheduled as soon as possible (but no later than 4 weeks from the Week **96** visit).

Section 4.6.1 Risk Assessment: Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)

Inadvertent Intravenous Injection (Accidental Maladministration)

Previously read:

The clinical consequences of overdose with ~~RPV LA~~ are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.

Now reads:

The clinical consequences of overdose with **CAB LA** are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.

Section 5.1 Inclusion Criteria #1

Previously read:

AGE
1. HIV-1 infected men or women aged 18 years or greater at the time of signing the informed consent

Now reads:

AGE
1. Aged 18 years or older (or ≥19 where required by local regulatory agencies), at the time of signing the informed consent.

Section 5.2 Exclusion Criteria #32

Previously read:

- Immunomodulators that alter immune responses (such as systemic corticosteroids, interleukins, or interferons. Note: Participants using short-term (<1 day) steroid tapers, topical, inhaled and intranasal corticosteroids are eligible for enrolment.

Now reads:

- Immunomodulators that alter immune responses (such as systemic corticosteroids, interleukins, or interferons. Note: Participants using short-term (≤14 days) steroid tapers, topical, inhaled and intranasal corticosteroids are eligible for enrolment.

Section 5.5.5.1 HIV-1 RNA Blips

Previously read:

Participants who have a HIV-1 RNA >50 c/mL and < 200 c/mL at key analysis timepoints (Week 48Week 96) must return to the clinic as soon as possible (but no later than 4 weeks after the date of the Week 48 or Week 96 visit) for a repeat HIV-1 RNA test such that the result falls within the same analysis window.

Now reads:

Participants who have a HIV-1 RNA ≥50 c/mL and < 200 c/mL at key analysis timepoints (Week 48, Week 96) must return to the clinic as soon as possible (but no later than 4 weeks after the date of the Week 48 or Week 96 visit) for a repeat HIV-1 RNA test such that the result falls within the same analysis window.

Section 6.13.2 Prohibited Medications and Non-Drug Therapies

Previously read:

Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Exclusion Criteria #30, Section 5.2).

Now reads:

Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Exclusion Criteria #32, Section 5.2).

Section 6.13.2 Prohibited Medications and Non-Drug Therapies

Previously read:

Chronic use of systemic (oral or parenteral) glucocortioids must be avoided due to immunosuppressive effect and potential decreases in RPV plasma concentrations; however, short treatment courses (e.g., 10 days or less) of oral prednisone/ prednisolone/methylprednisolone are allowed

Now reads:

Chronic use of systemic (oral or parenteral) glucocortioids must be avoided due to immunosuppressive effect and potential decreases in RPV plasma concentrations; however, short treatment courses (e.g., ≤ 14 days) of oral prednisone/ prednisolone/methylprednisolone are allowed

Section 7.1 Time and Events Table

Added check mark to IM treatment administration in column containing Weeks 64, 72, 84, and 92.

Section 7.1 Time and Events Table footnote J.

Previously read:

j. On Day 1, the eC-SSRS is to be administered prior to randomization. The eC-SSRS will be administered at each Q4W injection visit through the Week 48 primary endpoint, followed by Q12W thereafter through Week 96 (Week 60, 72, 74, 96). The eC-SSRS will preferably be completed at the beginning of the visit.

Now reads:

j. On Day 1, the eC-SSRS is to be administered prior to randomization. The eC-SSRS will be administered at each Q4W injection visit through the Week 48 primary endpoint, followed by Q12W thereafter through Week 96 (Week 60, 72, 84, 96). The eC-SSRS will preferably be completed at the beginning of the visit.

Section 7.1 Time and Events Table footnote 0.

Previously read:

o. Only collect if the Withdrawal visit occurs at Week 24, 48, or 96.

Now reads:

o. Only collect if the Withdrawal visit occurs at Week 48, or 96.

Section 7.3.3 HIV Associated Conditions

Previously read:

HIV-associated conditions will be recorded as per Time and Events schedule (Section 6). HIV-associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection (see Section 12.4).

Now reads:

HIV-associated conditions will be recorded as per Time and Events schedule (Section 7.1). HIV-associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection (see Section 12.4).

Section 7.4.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Previously read:

The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 12.6.2)

Now reads:

The investigator determines that the event or outcome qualifies as an SAE under part 'other situations' of the SAE definition (see Section 12.6.2)

Section 7.4.10 Suicidal Risk Monitoring

Section 7.4.10 has been deleted as duplicative of Section 7.4.5 Suicidal Risk Monitoring.

Appendix 8 Country Specific Requirements:

Appendix 8 has been added including the following text:

In this study subject identification number and visit number will not be included in the IP label. However, it will be tracked at site pharmacy when the IP is dispensed to each subject. (Note: This is an open label study, thus treatment number is not applicable.)

The investigational product (IP) labels have been added to Appendix 8, Section 12.8.1.

Amendment 02: A Sweden country specific amendment in response to queries from the Medical Products Agency.

12.9.2. Summary of Changes in Protocol Amendment 02 and Rationale

Changes were made to the protocol text in the following sections

- Protocol Synopsis-Dose Modifications; Section 4.3.5 Dose Modifications, and Section 6.8.1 Oral Bridging: Text has been adjusted to indicate that consultation with the Medical Monitor should occur prior to the implementation of an oral bridging strategy and for treatment guidance in the event of a missed dose with investigational product.

- Section 4.1 Overall Study Design: Additional details are provided regarding the timing of the planned IDMC analysis prior to participant transition into the Extension Phase.

- Section 5.1 Inclusion Criteria, Informed Consent: Details of Informed consent process updated to address that enrolment of participants who are unable to provide direct informed consent is optional and will be based on local legal/regulatory requirements and site feasibility to conduct protocol procedures.

- Section 6.7 Compliance with Study Treatment Administration: Additional text has been added regarding Investigator and site obligations to maximize patient compliance for both study arms and for the duration of the trial through the Follow-up Phase.

- Section 6.8.1 Oral Bridging: Clarifications were made within the text regarding the appropriate consultation procedures with the Medical Monitor for considerations of Oral Bridging and missed doses of the investigational product.

- Section 6.13.1 Concomitant Medications and Non-Drug Therapies: Additional text was added for guidance on concomitant medication use with rilpivirine.

- Section 7.4.3.4 Prompt Reporting of Serious Adverse Events and Other Events; Table 7 footnotes were updated to provide additional guidance on reporting guidelines for cardiovascular and death events

- Section 10.2, Regulatory and Ethical Considerations, Including the Informed Consent Process: Additional language clarifications and internal protocol references are provided.

- Section 10.4 Quality Assurance: Specification of quality assurance items required prior to study start has been added.

List of Changes

Protocol Synopsis, Treatment Arms and Duration, Dose modifications; and Section 4.2.5 Dose Modifications:

Previously Read:

In exceptional circumstances, the Medical Monitor may authorize the use of oral CAB and/or RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. Should a participant need "oral bridging", sites must contact the Medical Monitor for authorization and guidance for treatment strategies prior to a missed CAB LA + RPV LA dose. Should a participant not notify the site in advance, the Medical Monitor must be contacted for further treatment guidance.

Now Reads:

In exceptional circumstances, and in consultation with the Medical Monitor, Investigators may provide oral CAB and/or RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. Should a participant need "oral bridging", sites must contact the Medical Monitor for guidance on treatment strategies prior to a missed CAB LA + RPV LA dose. Should a participant not notify the site in advance, the Medical Monitor must be contacted for further treatment guidance.

Section 4.1 Overall Study Design

Previously read:

An Independent Data Monitoring Committee (IDMC) will evaluate interim efficacy, tolerability, safety and PK of CAB LA + RPV LA at predefined times during the study. An interim futility analysis will be performed for the IDMC with the intent of having approximately 50% of participants reaching Week 24.

Now reads:

An Independent Data Monitoring Committee (IDMC) will evaluate interim efficacy, tolerability, safety and PK of CAB LA + RPV LA at predefined times during the study. An interim futility analysis will be performed for the IDMC with the intent of having approximately 50% of participants reaching Week 24 with the intent to complete this analysis prior to any participants transitioning to the Extension Phase at Week 52. In addition, ad hoc IDMC reviews of safety and efficacy data would also be triggered if the number of virologic failures exceeds pre-specified thresholds as per the IDMC charter.

Section 5.1 Inclusion Criteria, Informed Consent

Previously read:

Capable of giving signed informed consent as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Eligible participants or their legal guardians must sign a written Informed Consent Form before any protocol-specified assessments are conducted.

Now reads:

Capable of giving signed informed consent as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Eligible participants or their legal guardians (and next of kin when locally required), must sign a written Informed Consent Form before any protocol-specified assessments are conducted. Enrolment of participants who are unable to provide direct informed consent is optional and will be based on local legal/regulatory requirements and site feasibility to conduct protocol procedures.

Section 6.7 Compliance with Study Treatment Administration

The following text was removed: ~~Treatment compliance will not be assessed during the Long-Term Follow-Up Phase.~~

Final paragraph previously read:

Due to the long acting nature of the CAB LA and RPV LA it will be imperative that the participant is compliant with dosing instructions. Investigators must have plans in place for adherence counselling for both treatment arms of the study. In addition, Investigators must have plans in place to perform visit reminders and to verify the participant's contact information at each visit.

Final paragraph now reads:

Due to the long acting nature of the CAB LA and RPV LA it will be imperative that the participant is compliant with dosing instructions. As part of the screening and participant selection, it is imperative that Investigators discuss with potential participants the long-term commitments for the trial, and the importance of adhering to treatment regimens. Sites are to have plans in place for adherence counselling for both treatment arms of the study for the duration of the study including the Long-Term Follow-Up Phase. In addition, Investigators must have plans in place to perform visit reminders, utilizing patient trackers provided by the study team as needed, and to verify the participant's contact information at each visit. Investigators should contact patients directly in the event that a participant misses any scheduled visit

Section 6.8.1 Oral Bridging

Previously read:

In exceptional circumstances, to address pre-planned missed CAB LA + RPV LA dosing visits, the medical monitor may authorize the use of daily oral CAB 30 mg and RPV 25mg as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. In certain circumstances (e.g., prior to steady state dosing and following a >4 week oral bridge) repeating the loading doses of CAB IM and RPV IM may be required. Should a participant require "oral bridging", sites must contact the medical monitor for authorization and guidance for treatment and dosing strategies prior to a missed CAB LA + RPV LA dose.

Now reads:

In exceptional circumstances, to address pre-planned missed CAB LA + RPV LA dosing visits, in consultation with the medical monitor, Investigators may provide daily oral CAB 30 mg and RPV 25mg as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. In certain circumstances (e.g., prior to steady state dosing and following a >4 week oral bridge) repeating the loading doses of CAB IM and RPV IM may be required. Should a participant require "oral bridging", sites must contact the medical monitor for guidance with treatment and dosing strategies prior to a missed CAB LA + RPV LA dose.

Section 6.13.1 Concomitant Medications and Non-Drug Therapies

The following text was added to the final paragraph of section 6.13.1:

Please refer to the local rilpivirine prescribing information for guidance regarding other drugs that are prohibited, should be used with caution, require dose adjustment, or increased clinical monitoring if taken with rilpivirine.

Section 7.4.3.4 Prompt Reporting of Serious Adverse Events and Other Events

Table 7 footnotes:

Previously Read

a. ABC HSR eCRF only required if event meets one of the ICH E2A definitions of seriousness.
b. GSK must be contacted at onset of liver chemistry elevations to discuss participant safety.
c. Liver event documents (i.e., "Liver Event eCRF" and updates, "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

a.

Now Reads:

a. Additional details and time frames for reporting cardiovascular and death events are provided in Section 7.4.3.7 and Section 7.4.3.8, respectively.
b. ABC HSR eCRF only required if event meets one of the ICH E2A definitions of seriousness.
c. GSK must be contacted at onset of liver chemistry elevations to discuss participant safety.

d. Liver event documents (i.e., "Liver Event eCRF" and updates, "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

Final Paragraph- Additional text was added:

Primary and secondary Medical Monitor/SAE contact information is provided on the Medical Monitor/Sponsor Information Page of the current protocol.

Section 10.2, Regulatory and Ethical Considerations, Including the Informed Consent Process:

Paragraph 3 Bullet number 2 was removed.

- ~~Obtaining signed informed consent~~

Paragraph 3 Bullet 4:

Previously Bullet 5 read:

- Signed informed consent must be obtained for each participant prior to participation in the study.

Current Bullet 4 now reads

- Signed informed consent must be obtained for each participant prior to participation in the study (see Inclusion Criteria, Section 5.1; Informed consent).

Section 10.4 Quality Assurance

The following language was added as the 3rd bullet:

Measures and documentation towards quality assurance that will be completed prior to study initiation will also include but not be limited to the study monitoring plan, study risk register, quality assurance plan, protocol deviation management plan, medical monitoring plan, and site feasibility assessments.

12.9.3. Summary of Changes in Protocol Amendment 03 and Rationale

The reasons for this amendment were to: update medical monitor/SAE contact information; provide additional clarity for assessments to be conducted during the Extension Phase; add text to instruct contact of the Medical Monitor upon the occurrence of rash during the CAB + RPV oral lead-in period; specify a secondary lipid objective and endpoint within the study objectives; provide clarity around dosing at the Day 1 visit; allow serum pregnancy testing instead of urine testing in the event that urine testing is not available; provide clarification that cabotegravir and rilpivirine exposure may persist for more than one year following IM injections, emphasize that participants should continue to use HAART for at least one year following the last CAB + RPV injection, and that

female participants of childbearing potential must continue to use adequate contraception for at least one year after the last CAB + RPV injection; expand the allowance of short treatment courses of topical, inhaled, or intranasal glucocorticoids to 21 days or less; add additional guidance for the definition of a change in ART regimen for inclusion/exclusion criteria; provide additional guidance on when to contact the Medical Monitor upon a serofast RPR result for screening syphilis test; clarify language within exclusion criteria #9; added text regarding the treatment assignment randomization schedule; remove a requirement to record within the eCRF how frequently IP was taken on average and the requirement to record any treatment delays or dose reductions of IP; add text to indicate that drugs known to cause Torsade des Pointes (TdP) should be used with caution with rilpivirine; remove limits on the duration for use of topical imiquimod; add clarity around reflexive testing for HBV DNA for participants with positive anti HBc and negative HBsAg and negative anti-HBs results; add temperature collection as part of vital signs to the Time and Events Table; add requirement that all sites should have a plan in place for managing possible risks for suicide related events; clarify text regarding PK sample window collection; clarify text for patient reported outcome endpoints and timings for completion of questionnaires relative to other clinical assessments and procedures, add clarification for prohibited medication information; remove information in the Appendix requiring collection of pregnancy information for female partners of male study participants; incorporate updates from country-specific amendments No 1, and No 2. into a global protocol amendment; add text that additional details of the injection device used by sites for IM administration including, but not limited to functional performance, may also be collected within the eCRF; clarify that commercially availability of CAB LA + RPV LA includes availability through local public/government health sectors; add allowance that in exceptional circumstances, local labs can be reviewed and approved by the Medical Monitor for consideration of participant eligibility; add other minor corrections and edits to protocol text.

List of Changes

Medical Monitor/Sponsor Information Page:

The Primary Medical Monitor, Secondary Medical Monitor, and SAE Contact information was updated from:

~~PPD MD, MPH~~
~~ViiV Healthcare~~
~~Research Triangle Park~~
~~Five Moore Drive, Research Triangle Park, NC 27709 (USA)~~
~~Mobile: PPD~~
~~Office Telephone: PPD~~
~~Fax: PPD~~
~~e-mail: PPD~~

~~**Secondary Medical Monitor:**~~

PPD ~~MD~~
~~ViiV Healthcare~~
~~Research Triangle Park~~
~~Five Moore Drive, Research Triangle Park, NC 27709 (USA)~~
~~Mobile:~~ PPD
~~Office Telephone:~~ PPD
~~Fax:~~ PPD
~~e-mail:~~ PPD

~~**Sponsor Serious Adverse Events (SAE) Contact Information:**~~

PPD ~~MD, MPH~~
~~ViiV Healthcare~~
~~Research Triangle Park~~
~~Five Moore Drive, Research Triangle Park, NC 27709 (USA)~~
~~Mobile:~~ PPD
~~Office Telephone:~~ PPD
~~Fax:~~ PPD
~~e-mail:~~ PPD

To:

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Protocol Synopsis and Protocol Section 3.0, Objectives and Endpoints:

The following Objective and Endpoint were added.

Objective	**Endpoint**
To evaluate the effects of CAB LA + RPV LA every 4 weeks on fasting lipids over time compared to continuation of current ART over time.	• **Change from Baseline in fasting lipids over time including Week 48 and Week 96.**

The following Objectives and Endpoints were updated:

Previously Read:

To assess the acceptance of pain and injection site reactions following injections	• ~~Dimension scores ("Bother of ISRs", "Leg movement", "Sleep", and "Acceptance)_ and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of iNjection questionnaire (PIN)~~
To assess degree of health-related quality of life ~~(HRQoL) using the HIV/AIDS-targeted quality of life (HAT-QoL) questionnaire short form~~	• ~~Summary statistics and between and within treatment group comparisons of change in HRQoL from Baseline and Weeks 24, 48, 96 (or Withdrawal).~~
To assess the health status ~~using the 12-item Short Form Health Survey (SF-12)~~	• ~~Summary statistics and between and within treatment group comparisons of change in health status from Baseline and Weeks 24,~~

	~~48, 96 (or Withdrawal)~~
To assess treatment satisfaction of CAB LA + RPV LA compared to continuation of current ART	• ~~Change from baseline in total "treatment satisfaction" score, and "pain discomfort" and "ease of administration" sub-scores of the HIVTSQs over time~~ • ~~Change in treatment satisfaction over time using the HIVTSQc at Week 48 (or Withdrawal)~~
To assess treatment acceptance ~~using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire which consists of 3 items grouped into one single score of overall acceptance~~	• ~~Summary statistics and between and within treatment group comparisons of change in treatment acceptance from Baseline and Weeks 8, 24, 48, 96 (or Withdrawal)~~
To assess tolerability of injections ~~using the Numeric Rating Scale (NRS) for patients randomized to the CAB + RPV LA arm.~~	• ~~Summary statistics, within treatment group comparisons and change in tolerability of injection from Weeks 4b, 5, 40, 41, and 96.~~
To assess treatment acceptance ~~using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire which consists of 3 items grouped into one single score of overall acceptance~~	• ~~Summary statistics and between and within treatment group comparisons of change in treatment acceptance from Baseline and Weeks 8, 24, 48, 96 (or Withdrawal)~~
~~To assess preference for CAB LA+ RPV LA compared to oral ARV using a single dichotomous preference question.~~	• ~~For patients randomized to the "CAB LA + RPV LA" arm, preference for CAB LA + RPV LA compared to oral ARV regimen, at Week 48~~ • ~~For patients randomized to the "Current ART" arm who switched to the injectable treatment, preference for CAB LA + RPV LA compared to current ART regimen at Week 96 (end of extension phase- secondary analysis)~~

Now Reads:

To assess the acceptance of pain and injection	• Change from Week 5 in Dimension scores

site reactions following injections	("Bother of ISRs", "Leg movement", "Sleep", and " Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of iNjection questionnaire (PIN)
To assess degree of health-related quality of life	• Change from Baseline in HR QoL using the HIV/AIDS-targeted quality of life questionnaire short form at Week 24, Week 48, Week 96 (or Withdrawal).
To assess the health status	• Change from Baseline in health status at Week 24, Week 48, and Week 96 (or Withdrawal) using the 12-item Short Form Survey (SF-12).
To assess treatment satisfaction of CAB LA + RPV LA compared to continuation of current ART	• Change from baseline in total "treatment satisfaction" score, and individual item scores of the HIVTSQs at Weeks 4b, 24, 44, 96 (or Withdrawal) • Change in treatment satisfaction over time using the HIVTSQc at Week 48 (or Withdrawal)
To assess treatment acceptance	• Change from Baseline in treatment acceptance at Week 8, Week 24, Week 48, Week 96 (or Withdrawal) using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire
To assess tolerability of injections	• Change from Week 4b in tolerability of injection at Week 5, Week 40, Week 41, and Week 96 using the Numeric Rating Scale (NRS) within the CAB + RPV LA arm.
To assess preference for CAB LA+ RPV LA compared to oral ARV	• For patients randomized to the "CAB LA + RPV LA" arm, preference for CAB LA + RPV LA compared to oral ARV regimen, at Week 48 using a single dichotomous

	preference question • For patients randomized to the "Current ART" arm who switched to the injectable treatment, preference for CAB LA + RPV LA compared to current ART regimen at Week 96 (end of extension phase- secondary analysis) using a single dichotomous preference question

Synopsis "Overall Design" and Section 4.1 Overall Design

The following text was added as the final sentence of paragraph two of the Synopsis "Overall Design", and Section 4.1:

Current ART dosing on Day 1 is recommended to occur after randomization to avoid overlap of regimens (in the event that the participant is assigned to the CAB LA + RPV LA treatment arm). However, if the participant takes current ART prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1.

The following text was added as the second sentence of paragraph three of the Synopsis "Overall Design", and Section 4.1:

At visit Week 4b, participants will return to the clinic, take the last dose of oral CAB + RPV, and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV).

Section 4.2.1 Screening Phase (Up to 35 days)

Second Paragraph

Previously Read

Participants will complete a screening period of up to 35 days. A single repeat of a procedure/lab parameter is allowed to determine eligibility (unless otherwise specified). Participants may be re-screened once which requires a new participant number. Participants who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be randomized as soon as all eligibility requirements have been confirmed at the site.

Now Reads:

Participants will complete a screening period of up to 35 days. A single repeat of a procedure/lab parameter is allowed to determine eligibility (unless otherwise specified). **In exceptional circumstances only, if a repeat lab is required because a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor for consideration of participant eligibility. A repeat central lab will be submitted concurrently or at the next planned visit.** Participants may be re-screened once which requires a new participant number. Participants who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be randomized as soon as all eligibility requirements have been confirmed at the site.

Section 4.2.2 Maintenance Phase (Day 1 up to Week 52)

The following text was added to the third complete paragraph:

If in the opinion of the Investigator, a participant experiences a significant safety event while taking oral CAB or RPV, administration of the first injections will be determined ONLY in consultation with the Medical Monitor. Any rash that is possibly related to study drug, and is present during the CAB + RPV oral lead-in period, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA (See Section 7.4.4.13).

Section 4.2.3.1 Participants Entering from the CAB LA + RPV LA Arm

First Paragraph

Previously Read:

All participants who successfully complete 52 weeks of CAB LA + RPV LA treatment in the Maintenance Phase will continue to have access to both CAB LA and RPV LA in the Extension Phase until study treatment is either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 4 weeks as per the Time and Events Schedule (Section 7.1)

Now Reads:

All participants who successfully complete 52 weeks of CAB LA + RPV LA treatment in the Maintenance Phase will continue to have access to both CAB LA and RPV LA in the Extension Phase until study treatment is either locally approved and commercially available **(including through local public/government health sectors),** the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 4 weeks as per the Time and Events Schedule (Section 7.1)

Section 4.2.3.2 Participants Entering from the current ART ARM

Second paragraph, third sentence

Previously Read:

In addition, central lab results and safety parameters from the Week 56a visit must be available and reviewed.

Now Reads:

In addition, central lab results and safety parameters from the Week 56a visit must be available and reviewed **before the Week 56b visit.**

Sixth Paragraph

Previously Read:

Participants will continue study treatment in the Extension Phase until CAB LA and RPV LA are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 4 weeks. See the Time and Events Table (Section 7.1) for more information.

Now Reads:

Participants will continue study treatment in the Extension Phase until CAB LA and RPV LA are either locally approved and commercially available **(including through local public/government health sectors),** the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 4 weeks. See the Time and Events Table (Section 7.1) for more information.

Section 4.2.4 Long-Term Follow-Up (LTFU) Phase – IM Regimen Only

Fourth paragraph, second sentence

Previously Read:

Female participants of child bearing potential must continue to use adequate contraception methods (see Study Procedures Manual [SPM] for list of accepted forms of contraception) for ~~the entire year of follow up.~~

Now Reads:

Female participants of child bearing potential must continue to use adequate contraception methods (see Study Procedures Manual [SPM] for list of accepted forms of contraception) for **at least 52 weeks after the last injection**.

Section 4.6.1 Risk Assessment Table; Development of Resistance following discontinuation of CAB LA.

First table column:

Previously Read:

Residual concentrations of CAB would remain in the systemic circulation of participants who stopped CAB LA treatment for prolonged periods (~~up to 1 year~~) despite stopping treatment (e.g., for tolerability issues or treatment failure).

Now Reads:

Residual concentrations of CAB would remain in the systemic circulation of participants who stopped CAB LA treatment for prolonged periods (**more than 1 year, in some subjects, GlaxoSmithKline Document Number 2016N269422_00**) despite stopping treatment (e.g., for tolerability issues or treatment failure). **Participants discontinuing CAB LA regimen may be at risk for developing HIV-1 resistance to CAB many weeks after discontinuing injectable therapy.**

Section 4.6.1 Risk Assessment Table; Oral CAB and CAB LA Drug-Drug Interactions

First table column, third complete paragraph

Previously Read:

Chronic use of oral glucocorticoids must be avoided; however, short treatment courses (for example, ~~14 days or less~~) and topical, inhaled or intranasal use of glucocorticoids will be allowed.

Now Reads:

Chronic use of oral glucocorticoids must be avoided; however, short treatment courses (for example, **21 days or less**) and topical, inhaled or intranasal use of glucocorticoids will be allowed.

Section 4.6.1 Risk Assessment Table; RPV LA; Development of Resistance

First table column, first paragraph

Previously Read:

Residual concentrations of RPV LA would remain in the systemic circulation of participants who stopped treatment (e.g., for tolerability issues or treatment failure) for prolonged periods (months).

Now Reads:

Residual concentrations of RPV LA can remain in the systemic circulation of participants who stopped treatment (e.g., for tolerability issues or treatment failure) for prolonged periods (months **to more than a year, in some subjects, McGowan, 2016**).

Section 5.1 Inclusion Criteria

3rd Paragraph

Previously Read:

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility.

Now Reads:

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility. **In exceptional circumstances only, if a repeat lab is required because a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor for consideration of participant eligibility. A repeat central lab will be submitted concurrently or at the next planned visit.**

Inclusion Criteria 2

Second paragraph, bullet #3

Previously read:

- Boosted PI (or atazanavir [ATV] unboosted) (~~either the initial or second PI-based cART regimen~~)

Now reads:

- Boosted PI (or atazanavir [ATV] unboosted) (**must be either the initial cART regimen or one historical within class switch is permitted due to safety/tolerability**)

The following text was also added to Inclusion Criteria 2 in order to provide additional guidance for the definition of a change in ART regimen:

The addition, removal, or switch of a drug(s) that has been used to treat HIV based on antiretroviral properties of the drug constitutes a change in ART with the following limited exceptions:

- **Historical changes in formulations of ART drugs or booster drugs, <u>will not</u> constitute a change in ART regimen if the data support similar exposures and efficacy, and the change must have been at least 3 months prior to Screening.**

- **Historical perinatal use of an NRTI when given in addition to an ongoing HAART will not be considered a change in ART regimen.**

- **A change in dosing scheme of the same drug from twice daily to once daily <u>will not</u> be considered a change in ART regimen if data support similar exposures and efficacy.**

Section 5.2 Exclusion Criteria

Exclusion Criteria 13

Previously Read:

13. All participants will be screened for syphilis (rapid plasma reagin [RPR]). Participants with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded. Participants with a positive RPR test who have not been treated may be rescreened at least 30 days after completion of antibiotic treatment for syphilis

Now Reads:

13. All participants will be screened for syphilis (rapid plasma reagin [RPR]). Participants with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded. **Participants with a serofast RPR result (persistence of a reactive nontreponemal syphilis test) despite history of adequate therapy and no evidence of re-exposure may enrol after consultation with the Medical Monitor.** Participants with a positive RPR test who have not been treated may be rescreened at least 30 days after completion of antibiotic treatment for syphilis

Exclusion Criteria 32, 5th bullet

Previously Read:

Immunomodulators that alter immune responses such as systemic corticosteroids, interleukins, or interferons. Note: Participants using short-term ~~(≤14 days)~~ ~~steroid tapers~~, topical, inhaled and intranasal corticosteroids are eligible for ~~enrollment.~~

Now Reads:

Immunomodulators that alter immune responses such as chronic systemic corticosteroids, interleukins, or interferons. Note: Participants using short-term (**e.g. ≤21 days**) **systemic corticosteroid treatment**; topical, inhaled and intranasal corticosteroids are eligible for **enrolment.**

Section 6.2 Treatment Assignment

The following text was added to the first paragraph:

The randomization schedule is comprised of a series of blocks, with equal treatment allocation within each block, which are shared across centres via central randomization. Given the open-label study design, central randomization was used to eliminate selection bias due to foreknowledge of randomized treatment. With central randomization, knowledge at a site of the randomized treatment group for

previous subjects does not predict which treatment group will be assigned to the next randomized subject.

Section 6.3 Dosage and Administration

Table 5 Dosage and Administration

Previously Read:

Current ART Arm*	
Day 1 to Week 52 (~~1 tablet once daily~~)	Take 2 NRTIs + INI **or** 2 NRTIs + NNRTI **or** 2 NRTIs + PI according to approved labeling.

Now Reads:

Current ART Arm*	
Day 1 to Week 52 (**Tablets daily**)	Take 2 NRTIs + INI **or** 2 NRTIs + NNRTI **or** 2 NRTIs + PI according to approved labeling. ***Take Day 1 dose after randomization**

Final Paragraph

Previously Read:

The CAB + RPV oral regimen should be administered together once daily at approximately the same time each day with a meal. ~~The participant will be asked how often IP was taken (with a meal) on average, since the last visit, and this information will be recorded in the eCRF.~~

Now Reads:

The CAB + RPV oral regimen should be administered together once daily at approximately the same time each day with a meal.

Section 6.6.1 Dosing Considerations for CAB LA + RPV LA

The following text was added to the end of the third paragraph:

Additional details of the injection device used by sites for IM administration including, but not limited to functional performance, may also be collected within the eCRF.Section 6.7 Compliance with Study Treatment Administration

Second Paragraph, last sentence:

Previously Read:

Treatment start and stop dates, ~~including dates for treatment delays and/or dose reductions~~ will also be recorded in the CRF.

Now Reads:

Treatment start and stop dates will also be recorded in the eCRF.

Section 6.9.1 IM Dosing, 1st paragraph, 4th sentence:

Previously Read:

Plasma concentrations of both drugs may be measurable for approximately 52 weeks than following IM injections.

Now Reads:

Plasma concentrations of both LA drugs may be measurable for more than one year following IM injections. **Any interruption in IM dosing should be discussed with the Medical Monitor. Investigators should ensure that the participant initiates alternative highly active ART to minimize the risk of developing resistance as concentrations of CAB and RPV decline over time. Section 6.13.1 Permitted Medications and Non-Drug Therapies**

The following text was added at the end of the section:

Drugs that cause Torsade des Pointes (TdP) should be used with caution when on rilpivirine (see SPM for list of drugs associated with TdP).

Section 6.13.2 Prohibited Medications and Non-Drug Therapies

3rd Bullet

Previously Read:

Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SPM). This includes topical agents with substantial systemic exposure and systemic effects. ~~Short term~~ use ~~(30 days or less)~~ of topical imiquimod is permitted.

Now Reads:

Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SPM). This includes topical agents

with substantial systemic exposure and systemic effects. **Use of topical imiquimod is permitted.**

5th Bullet

Previously Read:

Chronic use of systemic (oral or parenteral) glucocortioids must be avoided due to immunosuppressive effect and potential decreases in RPV plasma concentrations; however, short treatment courses ~~(e.g., ≤ 14 days)~~ of oral prednisone/ prednisolone/methylprednisolone are allowed. A single dose of systemic dexamethasone is permitted (more than a single dose may cause significant decrease in RPV plasma concentration and is prohibited), ~~and~~ topical, inhaled or intranasal use of glucocortioids will be allowed.

Now Reads:

Chronic use of systemic (oral or parenteral) glucocortioids must be avoided due to their immunosuppressive effect and potential decreases in RPV plasma concentrations; however, short treatment courses with oral prednisone/ prednisolone/methylprednisolone **(e.g. adjunctive treatment of Pneumocystis pneumonia with ≤ 21 days of tapering prednisone)** are allowed. A single dose of systemic dexamethasone is permitted (more than a single dose in a treatment course may cause significant decrease in RPV plasma concentration and is prohibited)**.** Topical, inhaled or intranasal use of glucocortioids will be allowed.

Section 7.1 Time and Events Table

The following text was added above the Time and Events Table:

Note: While some assessments included in the Time and Events Table are conducted less frequently following the secondary endpoint (Week 96), IM injections for participants randomized to CAB LA + RPV LA (and for participants who switch to CAB LA + RPV LA during the Extension Phase) will continue to be administered Q4W. Beginning after Week 96, the schedule of assessments for all participants will be modified to collect clinical chemistries, HIV-1 RNA, and CD4+ cell count every 12 weeks.

From Week 60 forward, all participants (from both originally randomized treatment arms), will have the same schedule of events (same visits, same assessments, same time frame).

Footnotes j, k, v, and aa were updated as follows:

Previously Read:

a. Complete all Screening assessments within 35 days. Participants may begin the Maintenance Phase as soon as all Screening assessments are complete. Participants may be rescreened once and will be assigned a new participant number.

j. On Day 1, the eC-SSRS is to be administered prior to randomization. The eC-SSRS will be administered at each Q4W injection visit through the Week 48 primary endpoint, followed by Q12W thereafter through Week 96 (Week 60, 72, 84, 96). The eC-SSRS will preferably be completed at the beginning of the visit.

k. Women of childbearing potential only. SR=serum, UR=urine. Pregnancy events will be captured starting at Day 1 following exposure to study drug.

v. With the exception of the NRS ~~and PIN~~, all Patient Report Questionnaires/Surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. NRS is to be given post injection. Only conduct questionnaires/surveys at Withdrawal if occurring prior to Week ~~48~~.

aa. "Perception of Injection questionnaire (PIN) to be administered following injections.

Now Reads:

a. Complete all Screening assessments within 35 days. Participants may begin the Maintenance Phase as soon as all Screening assessments are complete. Participants may be rescreened once and will be assigned a new participant number. **HLA-B*5701 result is not required to inform eligibility status.**

j. On Day 1, the eC-SSRS is to be administered prior to randomization. The eC-SSRS will be administered at each Q4W injection visit through the Week 48 primary endpoint, followed by Q12W thereafter through Week 96 (Week 60, 72, 84, 96). The eC-SSRS will preferably be completed at the beginning of the visit **following administration of other PROs required prior to injections.**

k. Women of childbearing potential only. SR=serum, UR=urine. Pregnancy events will be captured starting at Day 1 following exposure to study drug. **Serum pregnancy test can substitute for urine pregnancy test if locally required but must be appropriately timed to confirm pregnancy status prior to randomization and first IM administration.**

v. With the exception of the NRS questionnaire, all Patient Report Questionnaires/Surveys are recommended to be administered via validated electronic site pad or paper instrument at the beginning of the visit before any other assessments are conducted **and prior to administration of the eC-CSSRS**. NRS is to be given post injection. Conduct questionnaires/surveys at Withdrawal if occurring prior to Week **96**.

Footnote aa has been removed.

Section 7.2.1 Screening Assessments

Paragraph 5

Previously Read:

Participants infected with HBV will not be enrolled in the study.

Now Reads:

Participants infected with HBV will not be enrolled in the study. **Evidence of HBV infection is based on the results of testing at Screening for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs), and HBV DNA. HBV DNA will only be performed for participants with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).**

Paragraph 7

Previously Read:

All participants will be screened for syphilis (rapid plasma reagin [RPR]) at Screening. Participants with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded. Participants with a positive RPR test who have not been treated may be rescreened at least 30 days after completion of antibiotic treatment for syphilis.

Now Reads:

All participants will be screened for syphilis (rapid plasma reagin [RPR]) at Screening. Participants with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded**. Participants with a serofast RPR result despite history of adequate therapy and no evidence of re-exposure may enrol after consultation with the Medical Monitor.** Participants with a positive RPR test who have not been treated may be rescreened at least 30 days after completion of antibiotic treatment for syphilis.

Section 7.4.1 Clinical Evaluations

Bullet 4

Previously Read:

- Vital signs will include systolic and diastolic blood pressure and heart rate collected after resting for about 5 minutes.

Now Reads:

- Vital signs will include systolic and diastolic blood pressure and heart rate collected after resting for about 5 minutes. **Temperature will also be collected**.

Bullet 10

Previously Read:

- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of CAB LA or RPV LA or as required by the Medical Monitor following a treatment interruption(s).

Now Reads:

- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of CAB LA or RPV LA or as required by the Medical Monitor following a treatment interruption(s). **If serum testing is required locally, the results should be available prior to the visit where urine testing is indicated per the Time and Events Schedule (Section 7.1).**

Table 6 Safety Laboratory Assessments

Footnote g was added to Table 6 and irrelevant abbreviations for IL-6, hs-CRP, sVCAM, and HOMA-IR were removed.

Now Reads:

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[c]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine clearance[b]
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			

Plasma HIV-1 RNA[e]
CD4+ and CD8+ cell counts [CD4/CD8 ratio][f]
Peripheral Blood Mononuclear Cells (PBMCs): Day 1, Week 96, Withdrawal only
Hepatitis B (HBsAg), anti-HBc, anti-HBsAg, and hepatitis C antibody (Screening)[g]
Rapid Plasma Reagin (RPR) (Screening and Baseline)
HLA-B*5701 (Screening only)
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)
Pregnancy test for women of childbearing potential[h]
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate
Genetics Sample
Renal biomarkers including Cystatin-C (blood), Retinol Binding Protein (RBP, blood/urine)[i]
Bone biomarkers including: Bone-specific alkaline phosphatase, procollagen type 1 N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D[i]
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO2 = carbon dioxide, HDL = high density lipoprotein, LDL = low density lipoprotein, HBsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [Levey, 2009].
c) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
d) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
e) For participants meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain genotype/phenotype data.
f) CD8+ cells will only be reported at Baseline, Day 1, Weeks 4b, 24, 48, and 96.
g) HBV DNA will only be performed for participants with a positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).
h) Urine pregnancy test/ serum pregnancy test will be performed according to the Time and Events Table (Section 7.1).
i) Since the intention is to utilize these biomarker data for research purposes, the sponsor will not be reporting the results of these assessments to the investigator, except for 25 hydroxy-vitamin D.

Section 7.4.5 Suicidal Risk Monitoring

First and second paragraphs

Previously Read:

Participants with HIV infection may occasionally present with 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 INIs. Additionally, depression and anxiety has been reported in some participants being treated with RPV. Therefore, it is appropriate to monitor participants prospectively for suicidal ideation and / or behavior before and during treatment. It is recommended that the Investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

~~Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.~~

Now Reads:

Participants with HIV infection may occasionally present with 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 INIs. Additionally, depression and anxiety has been reported in some participants being treated with RPV. Therefore, it is appropriate to monitor **and closely observe** participants prospectively **before and during treatment** for suicidal ideation and/or behavior, **or any other unusual changes in behavior**. It is recommended that the Investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

The following text was added to the end of paragraph 4:

All sites should have a plan in place for managing possible risks for suicide related events.

Section 7.5.1 PK Sample Collection

The first paragraph below Table 8, CAB and RPV Plasma Pharmacokinetic Sample Schedule

Previously Read:

~~PK window for sample collection~~: Pre-dose visits: ±3 days (1st injection), minus 7 days (2nd and 3rd injections), and ± 7days (4th and all subsequent injections); 2 hours post dose: ± one hour; one week post dose visits (Week 5 and Week 41): 3-10 days post injection.

Now Reads:

PK visit window and sample collection: Pre-dose **visits (from projected visit date):** +/- 3 days (1st injection), minus 7 days (2nd and 3rd injection), and +/- 7days (4th and all subsequent injections); **Pre-dose sample collection at Week 4b (and Week 56b for participants transitioning from the current ART arm): 20 to 28 hours after the last oral dose of CAB and RPV was taken**; 2 hours post dose: +/-one hour; one week post dose visits: 3 to 10 days post injection.

Section 7.9 Value Evidence and Outcomes

First paragraph

Previously Read:

Health outcomes assessments will be conducted according to the Time and Events Table (Section 7.1). Assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments.

Now Reads:

Health outcomes assessments will be conducted according to the Time and Events Table (Section 7.1). Assessments are recommended to be administered **with an electronic site pad or paper instrument** at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments **with the exception of the NRS (administered post injection).**

Section 7.9.1 Value Evidence and Outcomes Endpoints (Secondary)

Previously Read:

- ~~Summary statistics and between and within treatment group comparisons will be assessed on change in treatment satisfaction (using the HIV-TSQs) from Baseline and Weeks 4b, 24, 48, 96 (or Withdrawal)~~

- ~~Between and within treatment group comparisons will be assessed on change in treatment satisfaction over time (using the HIV-TSQc) at Week 48 (or Withdrawal from the study)~~

- ~~Summary statistics and between and within treatment group comparisons will be assessed on change in treatment acceptance from Baseline (using the ACCEPT) and Weeks 8, 24, 48, 96 (or Withdrawal)~~

- ~~Summary statistics and between and within treatment group comparisons will be assessed on change in the broader impact on health status (using the SF-12) from Baseline and Weeks 24, 48, 96 (or Withdrawal)~~

- ~~Summary statistics and between and within treatment group comparisons will be assessed on change in HRQoL (using the HAT-QoL short form) from Baseline and Weeks 24, 48, 96 (or Withdrawal)~~

- ~~Summary statistics and within treatment group comparisons will be assessed on acceptance of pain and injection-site reactions following injections (using the PIN) at weeks 5, 41, 48, 96 (or Withdrawal from the study) on patients randomized to the "CAB LA + RPV LA" arm.~~

- ~~Summary statistics and within treatment group comparisons will be assessed on the tolerability of injections (using the NRS) at Weeks 4b, and 40, and 96 and for one week post injection visits at Weeks 5, and 41 for participants randomized to the CAB LA and RPV LA arm. Change in tolerability of injection will be assessed from Baseline and Week 48 (primary analysis), and from Baseline and Week 96 (secondary analysis)~~

Now Reads:

- **Change from Week 5 in Dimension scores (e.g., "Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of iNjection questionnaire (PIN).**

- **Proportion of participants considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the Perception of iNjection questionnaire (PIN).**

- **Change from baseline in total "treatment satisfaction" score, and individual item scores of the HIVTSQs at Weeks 4b, 24, 44, 96 (or Withdrawal).**

- **Change in treatment satisfaction over time (using the HIVTSQc) at Week 48 (or Withdrawal).**
- **Change from Baseline in treatment acceptance (at Weeks 8, 24, 48, 96 (or Withdrawal from the study) using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire.**
- **Change from Baseline in health status at Week 24, Week 48, and Week 96 (or Withdrawal) using the 12-item Short Form Survey (SF-12).**
- **Change from Baseline in HR QoL (using the HAT-QoL short form) at Weeks 24, 48, 96 (or Withdrawal from the study).**
- **Change from Week 4b in tolerability of injections (using the NRS) at Weeks 5, 40, 41, 96.**

Section 11, References

The following references were added:

GlaxoSmithKline Document Number 2016N269422_00: 201120: A Phase IIa Study to Evaluate the Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, GSK1265744, in HIV Uninfected Men (ÉCLAIR) – Week 81 Results. Effective Date: 25Oct2016.

McGowan I, Siegel A, Engstrom J, et al. Persistence of rilpivirine following single dose of long-acting injection. 21st International AIDS Conference (AIDS 2016). July 18-22, 2016. Durban, South Africa. Abstract TUAC0103.

Section 12.7.2 Collection of Pregnancy Information

The following text was removed:

- ~~Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who are randomized to receive study medication.~~
- ~~After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy~~
- ~~Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.~~
- ~~Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.~~

12.9.4. Protocol Amendment 4 Summary of Changes Table

Overall Rationale Amendment 4: Protocol amendment #4 applies to all sites. The reason for amendment 4 is to acknowledge the potential rollover of eligible 201585 (ATLAS) study participants following the Week 52 visit and completion of the primary endpoint to the 207966 (ATLAS-2M) study. Specifications for the procedural rollover of 201585 participants are included within amendment #4. Due to the planned transition of eligible participants to ATLAS-2M following the Week 48 primary endpoint, the snapshot virologic response Week 96 for ATLAS is no longer valid and has been replaced with the proportion of participants with plasma HIV-1 RNA <50 c/mL over time including Week 96. Updated references for the cabotegravir and rilpivirine investigator brochures have also been added.

Section # and Name	Description of Change	Brief Rationale
Section 3: Objectives and Endpoints and corresponding text in Sections 4.2.3, 5.5.5.1, 9.4.9,	Removal of secondary endpoints based on the snapshot virologic response and subgroup analyses at Week 96. A secondary endpoint including the Proportion of participants with plasma HIV-1 RNA <50 c/mL over time including Week 96 (Observed Case) is added to replace the analysis by Snapshot virologic response	Due to the planned transition of eligible participants following the primary endpoint of ATLAS to the 207966 (ATLAS-2M) study examining the efficacy, safety and tolerability of CAB LA + RPV LA administered every 4 weeks (Q4W) compared to CAB LA + RPV LA administered every 8 weeks (Q8W), the snapshot virologic response Week 96 for ATLAS is no longer valid and has been replaced with the proportion of participants with plasma HIV-1 RNA < 50 c/mL over time including Week 96. Insufficient participant numbers are anticipated at Week 96 to support subgroup analyses as originally planned.
Synopsis, and Section 4.3: 207966 (ATLAS-2M) Rollover Option.	Addition of text describing the 207966 (ATLAS-2M) rollover option upon individual participant completion of the ATLAS primary endpoint.	Text added acknowledges the potential rollover of eligible 201585 (ATLAS) study participants following the Week 52 visit and completion of the primary endpoint to the 207966 (ATLAS-2M) study.
Section 4.3:1 201585 (ATLAS) to 207966 (ATLAS-2M) Transition Strategy	Addition of text describing the ATLAS to ATLAS-2M transition strategy for subgroups of patients	Offers guidance including appropriate timing for the transition of eligible ATLAS participants to ATLAS-2M upon local approval and implementation of ATLAS-2M

Synopsis and Section 5.6 Participant and Study Completion	Revision of the study completion definition	The definition for study completion has been updated to acknowledge and accommodate the optional rollover of participants from ATLAS to ATLAS-2M, thereby enabling appropriate generation of participant disposition data. Participants from either treatment arm who complete study Week 52 or enter and complete the Extension Phase will be considered to have completed the study.
Sections 7.4.3.4 (Table 7), 7.4.6.3, and 12.7.2: Reporting of Serious Adverse Events and Other Events	Initial report of pregnancy and completion of Pregnancy Notification Form has been updated to within 24 hours of identification of a Pregnancy event. Follow-up Pregnancy form (and SAE if required) has been updated to within 24 hours of investigator awareness of pregnancy outcome. Text Update: Suspected ABC HSR in participants randomized to the current ART arm or receiving Oral SOC during the Long-Term Follow-Up Phase	Reporting timelines and documentation requirements have been updated to reflect current Sponsor requirements Clarification for reporting suspected ABC HSR adverse event also applies during the Long-Term Follow-Up Phase for participants returning to Oral Standard of Care
Section 11. References	Updated references for the cabotegravir and rilpivirine investigator brochures have also been added.	Updated references
General Body Text	Minor clarifications with body text are made to assist with reader comprehension	Clarifications