TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase III, Randomized, Multicenter, Parallel-group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability of Long-Acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch from an Integrase Inhibitor Single Tablet Regimen in HIV-1 Infected Antiretroviral Therapy Naive Adult Participants

Compound Number: GSK1265744

Development Phase: IIIA

Effective Date: 24-SEP-2018

Protocol Amendment Number: 04

Author (s): PPD
PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N248866_00	2016-MAY-26	Original
2015N248866_01	2016-DEC-13	Amendment No. 1
The reasons for this amendment were to: added new primary Medical Monitor contact information; added lipid objective and endpoint back in to the table within the Synopsis section; added clarification of text for patient reported outcome endpoints; added additional clarification regarding provision of CAB LA and RPV LA until available through public/government health sectors; new text added to allow use of local labs to determine eligibility in exceptional circumstances; updated Time and Events Table to provide more clarity around assessments conducted during the Extension Phase, added 'X' to include collection of cardiovascular risk information at Screening, added temperature to Vital Signs row, added row for randomization, and clarified timings for completion of patient reported questionnaires relative to other clinical assessments in the table footnotes; clarified timing of dosing for abacavir/dolutegravir/lamivudine (ABC/DTG/3TC, Triumeq) for the Day 1 visit; added additional clarification that participants of child bearing potential must continue contraception for at least 52 weeks after the last injection; revised text to say that Investigators may provide 'bridging' supply after consultation with Medical Monitor (vs Medical Monitor authorizing bridging supply); provided clarification that cabotegravir and rilpivirine exposure may persist for more than one year in some participants after intramuscular administration (with added references); minor edits to prohibited medication information; added statement that drugs that cause Torsade de Pointes should be used with caution when taking rilpivirine; additional clarification that background NRTI therapy is not considered Investigational Product and accountability will not be done for NRTI background; changed film coat color for Tivicay (dolutegravir) from white (clinical trial material supply) to yellow (commercial supply) and removed statement to "protect from light" (for both Triumeq and Tivicay); sentence added for collection of additional details for the injection device used for IM administration; additional information included regarding randomization schedule; added text stating the investigator must discuss long-term commitment for the study with potential participants; added statement regarding serofast RPR results; allowed serum pregnancy testing where required locally (e.g. when urine testing is not available); removed duplicate text regarding monitoring for suicidal related events; added option for patient reported outcomes to be collected on paper instrument if needed; removed information in Appendix requiring collection of pregnancy information for female partners of male study participants; definition of ACCEPT, HIVTSQc, and HIVTSQs added to abbreviations table, duplication of ICH abbreviation removed; other minor corrections (e.g., updated references, adding cross reference to sections, correction of hyperlink to one table).		
2015N248866_02	2017-JUL-19	Amendment No. 2
The reasons for this amendment are as follow: update of contact information for		

secondary Medical Monitor; modify text to allow dose reduction for participants who have a decline in creatinine clearance to <50 mL/min; clarify that for participants not eligible to continue into the Maintenance Phase, only samples with HIV-1 RNA > 400 c/mL will be sent for resistance testing; add mitigation for ECG pad removal; clarify ± 3 day window is for all oral dosing (both Induction and Maintenance Phase); add "LA Arm" back to columns for Week 68, 76, 84, 92 on Time and Events Schedule (hidden when column was narrowed); clarify Week 104b visit is specific to those participants transitioning from oral IP to CAB LA + RPV LA; clarification added to footnote 'p' that genetics sample can be collected at any visit after signing informed consent, but Week [-20] preferred; correct footnote on Week 5 visit to reflect footnote 't'; add footnote 'y' back to Time and Events column for Withdrawal Visit (for Induction Phase); add clarification to Time and Events column that ISR assessments are only conducted for subjects receiving injections. Administrative typographical errors corrected (e.g. clarification provided regarding genetics sample taken after participants are enrolled into the study [vs when participants are randomized]), and investigator brochure references updated, references added.		
2015N248866_03	2018-JUN-25	Amendment No. 3
Changes for Amendment 3 were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defect in infants born to women with exposure to dolutegravir (DTG) at the time of conception. • A Risk Assessment table was added to include language regarding risk and mitigation of neural tube defects seen with DTG. • The withdrawal criteria were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant should also be withdrawn from the study. • The Time and Events table was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy. Additionally, clarifications were provided for the following: • the DTG IB should be referenced for additional risks, safety information, drug interactions, etc.; • 'suspected' was added to the text prior to the bulleted definition of suspected virologic failure in Section 5.4.5.3.; • specific storage conditions were removed from the protocol for IP, and a statement added to store according to product label; • insulin was removed from the section regarding clinical assessments performed during the study; • timeframe for pregnancy reporting and follow-up were updated to 24 hours to align with current reporting process; • prescribing information and IB references were updated.		
2015N248866_04	2018-SEP-24	Amendment No. 4
The primary reason for protocol amendment 04 is to allow an optional (vs mandatory) oral lead-in for participants randomized to the ABC/DTG/3TC arm who choose to		

continue into the Extension Phase of the study and receive CAB LA + RPV LA. The Appendix for contraceptive guidance and collection of pregnancy information was updated to be consistent with current protocol template text. Other minor clarifications were made as needed, e.g., the eCSSRs timing in the footnote for the Time and Events Table, updated abbreviations, etc.

SPONSOR SIGNATORY

PPD

Sept 24, 2018

PPD

Kimberly Smith, MD, M
VP, Global Medical Strategy
ViiV Healthcare

Date

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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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This study is sponsored by ViiV Healthcare. GlaxoSmithKline is supporting ViiV Healthcare in the conduct of this study.

Sponsor Name and Legal Registered Address (excluding US):

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Note: In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Vice President, Global Medical Strategy.

Regulatory Agency Identifying Number(s):

US IND: 109,678

EudraCT #: 2016-001646-25

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201584

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 201584

Rationale

201584 (the First Long-Acting Injectable Regimen – FLAIR study) is being conducted to establish if human immunodeficiency virus type-1 (HIV-1) infected adult participants whose virus is virologically suppressed on an integrase inhibitor single tablet regimen (INI STR) will remain suppressed after switching to a two-drug intramuscular (IM) long-acting (LA) regimen of cabotegravir (CAB) and rilpivirine (RPV). In this study, the INI STR will be limited to abacavir/dolutegravir/lamivudine (ABC/DTG/3TC). This study is designed to demonstrate the non-inferior antiviral activity of switching to a two drug CAB LA 400 mg + RPV LA 600 mg regimen every 4 weeks (Q4W: monthly) compared to remaining on ABC/DTG/3TC over 48 weeks (4 weeks oral CAB + RPV, 44 weeks LA therapy). 201584 (FLAIR) will also allow for characterization of long-term antiviral activity, safety, and tolerability and participant satisfaction of the regimens through Week 96. Additionally, participants randomized to continue ABC/DTG/3TC will be given an option to switch to LA therapy at Week 100. Eligible participants (HIV-1 ribonucleic acid [RNA] <50 c/mL at Week 96) would transition to LA dosing, beginning with the first IM CAB LA + RPV LA injections at either Week 100 (direct to injection) or Week 104b (following optional oral lead-in with CAB 30 mg and RPV 25 mg).

201584 (FLAIR) is being conducted in parallel with the 201585 (ATLAS) study with the aim to pool data generated from the current study with study 201585, 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 ABC/DTG/3TC over 48 weeks in HIV-1 antiretroviral naïve participants.	• Proportion of participants with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 48 (Missing, Switch, or Discontinuation = Failure, 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 ABC/DTG/3TC.	• Proportion of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm (Intent-to-Treat Exposed [ITT-E] population). • Proportion of participants with plasma HIV-1 RNA <200 c/mL at Week 48 using the FDA Snapshot algorithm (ITT-E population). • Proportion of participants with plasma HIV-1 RNA <200 c/mL and HIV-1 RNA <50 c/mL at Week 96 using the FDA Snapshot algorithm (ITT-E population).

Objectives	Endpoints
	• Proportion of participants with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 96. • Proportion of participants with confirmed virologic failure at Week 48 and Week 96. • Absolute values and change from Baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Week 48 and Week 96. • Absolute values and changes from Baseline in CD4+ cell counts over time including Week 48 and Week 96. • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death).
To evaluate the safety and tolerability of switching to CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of ABC/DTG/3TC over time.	• Incidence and severity of adverse events (AEs) and laboratory abnormalities over time including Week 48 and Week 96. • Proportion of participants who discontinue treatment due to AEs over time including Week 48 and Week 96. • Absolute values and changes in laboratory parameters over time including Week 48 and Week 96.
To evaluate the effects of CAB LA + RPV LA every 4 weeks on fasting lipids over time compared to continuation of ABC/DTG/3TC over time.	• Change from Baseline in fasting lipids over time including Week 48 and Week 96.
To assess the development of 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 and Week 96.
To characterize CAB and RPV concentrations and population pharmacokinetics (PK) 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 (BMI), and relevant laboratory parameters will be evaluated as potential predictors of inter- and intra-participant

Objectives	Endpoints
	variability for pharmacokinetic parameters.
To assess the acceptance of pain and injection site reactions following injections.	• 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).
To assess treatment satisfaction of CAB LA + RPV LA compared to continuation of ABC/DTG/3TC.	• Change from baseline in total "treatment satisfaction" score, and individual item scores of the HIV Treatment Satisfaction Questionnaire (status version) (HIVTSQs) at Week 4b, Week 24, Week 44, Week 96 (or Withdrawal). • Change in treatment satisfaction over time (using the HIVTSQc change version [HIVTSQc]) at Week 48 (or Withdrawal).
To assess degree of health-related quality of life (HR QoL).	• Change from Baseline in HR QoL using the HIV/AIDS targeted quality of life questionnaire (HAT-QoL) short format Week 24, Week 48, Week 96 (or Withdrawal).
To assess 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 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 injections at Week 5, Week 40, Week 41, and Week 96 using the Numeric Rating

Objectives	Endpoints
	Scale (NRS) within the CAB LA + RPV LA arm.
To evaluate the antiviral and immunologic effects, safety and tolerability, and development of viral resistance to CAB LA + RPV LA at Week 124 and over time for participants switching from ABC/DTG/3TC in the Extension Phase, *with and without optional oral lead-in.*	• Proportion of participants with HIV-1 RNA $\geq$ 50 c/mL at Week 124, with and without oral lead-in (FDA Snapshot algorithm, Extension Switch population). • Proportion of participants with plasma HIV-1 RNA <50 c/mL and HIV-1 RNA <200 c/mL over time. • Proportion of participants with confirmed virologic failure over time. • Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV over time. • Absolute values and change from Baseline in CD4+ cell counts over time. • Incidence and severity of AEs and laboratory abnormalities over time. • Proportion of participants who discontinue treatment due to AEs over time. • Absolute values and change in laboratory parameters over time.
To evaluate the pharmacokinetics of CAB and RPV in the setting of no oral lead-in for participants switching from ABC/DTG/3TC in the Extension Phase.	• To evaluate plasma CAB and RPV concentrations over time (Week 100 [direct to inject without oral lead-in] and Week 104 [both direct to inject and optional oral lead-in participants])
Exploratory	
To explore the effect of participant characteristics on the virologic and immunologic response of CAB LA and RPV LA compared to continuation of ABC/DTG/3TC.	• 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, and 96 using the Snapshot algorithm for the ITT-E population. • Proportion of participants by subgroup(s) (e.g. by age, gender, BMI, race, HIV-1 subtype, Baseline CD4+) with plasma HIV-1 RNA <50 c/mL at Week 48 and Week 96. • Change from Baseline in CD4+ cell counts

Objectives	Endpoints
	by subgroups at Week 48 and Week 96.
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 receiving CAB LA and RPV LA compared to continuation of ABC/DTG/3TC over time.	• Absolute values and change from Baseline in renal (in urine and blood) and bone (in blood) biomarkers over time including Week 48 and Week 96.
To assess preference for CAB LA + RPV LA compared to oral antiretroviral (ARV) therapy using a single dichotomous preference question.	• For participants randomized to the "CAB LA + RPV LA" arm, preference for CAB LA + RPV LA compared to oral ARV regimen, at Week 48.

Overall Design

201584 (FLAIR) is a 120-week Phase 3, multi-phase, randomized, open label, active-controlled, multicenter, parallel-group, non-inferiority study in HIV-1, ART-naïve adult participants. Participants who fulfill eligibility requirements will enroll into the Induction Phase of the study and receive ABC/DTG/3TC for 20 weeks (Week [-20] to Day 1). Participants who have an HIV-1 RNA <50 c/mL at Week (-4) will be randomized (1:1) into the Maintenance Phase at Day 1 to either continue ABC/DTG/3TC or to discontinue ABC/DTG/3TC and begin oral therapy with CAB 30 mg + RPV 25 mg once daily. ABC/DTG/3TC dosing on Day 1 should 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 ABC/DTG/3TC prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1. Participants who are not eligible to continue into the Maintenance Phase will be withdrawn from the study. At the Week 4a visit, assessments (including e.g., clinical chemistries) will be performed. 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 Week 4b visit can be performed as soon as central laboratory results become available and safety parameters are reviewed. The second and third IM injections (CAB LA 400 mg + 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 injections occur within the window of Week 7 to Week 8, but not later than Week 8, and the third injections occur within the window of Week 11 to Week 12, but no later than Week 12. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks (monthly) thereafter, with a ± 7 day dosing window being allowed (but not preferred). In addition, starting at the Week 12 injections, the interval between injection visits should be limited to a maximum of 5 weeks. If the length of time between injections exceeds, or is projected to exceed 5 weeks, the Medical Monitor must be contacted to discuss individual participant case management.

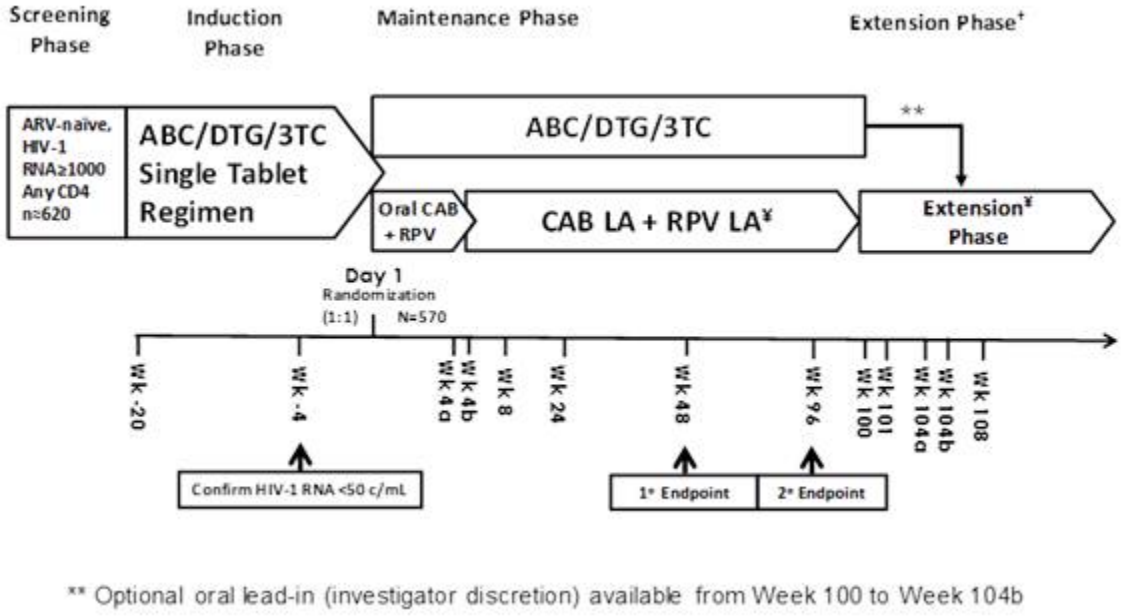
Participants randomized to ABC/DTG/3TC during the Maintenance Phase will continue ABC/DTG/3TC for at least an additional 100 weeks. Participants who successfully complete Week 100 (without meeting study defined withdrawal criteria and who remain virologically suppressed: HIV-1 RNA <50 c/mL) will be given the option to switch to the LA arm in the Extension Phase or be withdrawn from the study.

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 will enter a 52 week Long-Term Follow-Up Phase. Participants must remain on suppressive highly active antiretroviral therapy (HAART) for at least 52 weeks after the last dose of CAB LA and/or RPV LA.

In order to achieve balance across the two treatment arms, randomization will be stratified by participants' Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) and gender at birth. The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criterion at Week 48. The proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 of maintenance treatment using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] population) is a key secondary endpoint comparison.

Assuming a 20% screen failure rate, sufficient ART-naïve participants will be screened (approximately 775) in order to ensure that a total of approximately 620 participants are enrolled at the beginning of the Induction Phase. Assuming 7.5% of enrolled participants will not participate in the Maintenance Phase, this will ensure approximately 570 participants continue into the Maintenance Phase. The sample size of 285 per arm (at Day 1) is such that the study has approximately 97% power to demonstrate non-inferiority in the proportion of participants with snaphot virologic failure at Week 48 using an 6% margin, assuming a true 3% failure rate for CAB LA + RPV LA and a 2% failure rate for the ABC/DTG/3TC control arm and using a 2.5% one-sided alpha level. This sample size is primarly chosen so that the pooled analysis of data from this study and study 201585 (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.

201584 (FLAIR) Study Schematic



** Optional oral lead-in (investigator discretion) available from Week 100 to Week 104b

¥Subjects who withdraw from IM CAB LA + RPV LA must enter the 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.

All participants will complete the Screening Phase of up to 35 days prior to Baseline (Week [-20]) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. Participants may be re-screened once. Participants who are enrolled into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be enrolled as soon as all eligibility requirements have been confirmed at the site.

Induction Phase (Week [-20] to Day 1)

Following the Screening Phase, eligible participants will be enrolled into the study and begin a 20 week Induction Phase on ABC/DTG/3TC. Participants who have demonstrated tolerability to the Induction Phase regimen and with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Phase. A single repeat HIV-1 RNA test to determine eligibility may be allowed ONLY after consultation with the Medical Monitor. The retest should be scheduled as soon as possible as results of this retest must be available prior to the Day 1 visit. Participants with HIV-1 RNA ≥400 c/mL at Week (-4) are not eligible to enter the Maintenance Phase, will not be allowed a repeat to determine eligibility, and will therefore be withdrawn from the study. Note: ABC/DTG/3TC dosing on Day 1 should 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 ABC/DTG/3TC prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1.

Maintenance Phase (Day 1 to Week 100)

At Day 1, the Maintenance Phase begins. 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, 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 Week 4b visit can be performed as soon as central laboratory results become available and safety parameters are reviewed. The second and third IM injections (CAB LA 400 mg + 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 injections occur within the window of Week 7 to Week 8, but not later than Week 8), and the third injections occur within the window of Week 11 to Week 12, but no later than Week 12. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, with a (+ or -) 7 day dosing window, from the projected visit date, being allowed (but not preferred). Following the Week 12 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.

  OR

- Continue on the oral ABC/DTG/3TC initiated during the Induction Phase for at least an additional 100 weeks. Participants who successfully complete Week 100 (without meeting study defined withdrawal criteria and who remain virologically suppressed through Week 96: 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.

- ABC/DTG/3TC dosing on Day 1 should occur after randomization to avoid overlap of regimens (in the event that the participant is assigned to begin oral CAB and RPV on Day 1). However, if the participant takes ABC/DTG/3TC prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned on Day 1.

Randomization will be stratified by participants' Baseline HIV-1 RNA (<100,000, ≥ 100,000 c/mL) and gender at birth.

Extension Phase

All eligible participants who transition into the Extension Phase 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.

Participants not eligible to enter the Extension Phase will end their study participation (Week 100 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.

Participants Entering from the CAB LA + RPV LA Arm

All participants who successfully complete Week 100 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.

Participants Entering from the ABC/DTG/3TC Arm

Participants randomized to continue ABC/DTG/3TC 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 100.

The transition from ABC/DTG/3TC to CAB LA + RPV LA within the Extension Phase can be completed with or without an oral lead-in prior to commencement of injectable treatment. The oral lead-in decision will be made by the participant in consultation with the investigator and must be appropriately documented. As participants approach the Week 100 visit, sites must ensure sufficient CAB and RPV supply are available to support the participant's decision for transition to LA.

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 ABC/DTG/3TC while eligibility is being confirmed.

All participants with an undetectable HIV-1 RNA (<50 c/mL) result from the Week 96 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 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 with a 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 96 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 Transitioning Direct to Injection in the Extension Phase

Central lab results and safety parameters from the Week 96 visit must be available and reviewed for participants who choose to transition direct to injection. Participants with ongoing safety issues or laboratory abnormalities of clinical concern (e.g., Grade 3 or

Grade 4 liver enzyme elevations), will require consultation and agreement with the Medical Monitor prior to proceeding directly to injections in the Extension Phase.

If a clinical chemistry retest is required based on Week 96 labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 96). Participants will remain on oral ABC/DTG/3TC until the Week 100 injection visit, and until any required Week 96 retest results are available for review.

At Week 100, eligible participants will take the last dose of ABC/DTG/3TC (or DTG + 2 NRTIs), and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg) as initial loading doses. Clinical chemistries will also be assessed at Week 100. At Week 101, participants will return to the clinic for PK and safety assessments including clinical chemistries. The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104a and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104a, but not later than Week 104a, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 108 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 Receiving Optional Oral Lead-In in the Extension Phase

At Week 100, eligible participants who after discussion with the investigator, choose to receive the optional oral lead-in will initiate a 4 week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily. It is not necessary to dose ABC/DTG/3TC on the day the participant begins the oral lead-in with CAB + RPV. However, if the participant takes ABC/DTG/3TC prior to coming into the clinic, initiation of oral CAB and RPV should continue as planned. Clinical chemistries will also be assessed at Week 100. At Week 104a, following the 4 week CAB + RPV oral lead-in, participants will have additional safety assessments including clinical chemistries. In addition, central lab results and safety parameters from the Week 104a visit must be available and reviewed. If a clinical chemistry retest is required based on Week 104a labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 104a). Participants will remain on oral CAB 30 mg + RPV 25 mg until the Week 104b injection visit, and until any required Visit 104a retest results are available for review. An HIV-1 RNA sample will not be collected at Week 104a for participants receiving the optional oral lead-in, but will be obtained at the Week 104b visit to serve as the injection baseline viral load.

At visit Week 104b, 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 Week 104b visit can be performed as soon as central lab results from the Week 104a visit become available and safety parameters are reviewed. The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 108 and Week 112. There will be a one week dosing window for the second and third IM injections such that the second injections

occur within the window of Week 107 to Week 108, but not later than Week 108, and the third injections occur within the window of Week 111 to Week 112, but no later than Week 112. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 112 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.

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 highly active antiretroviral therapy (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 non-nucleoside reverse transcriptase inhibitor (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 four weeks of the last injection.

- The 52 weeks follow up phase will begin the day of the last CAB LA and/or RPV LA dose. These participants will not complete a Withdrawal visit, but will instead move directly into the Long-Term Follow Up Phase.

- Participants will be assessed with clinic visits at Months 1, 3, 6, 9 and 12. Female participants of child bearing potential must continue to use adequate contraception methods 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, GlaxoSmithKline (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 the withdrawal visit.

Protocol Permitted Substitutions

Participants who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on DTG and an approved dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone that does not contain abacavir (e.g. tenofovir/emtricitabine [TDF/FTC] or tenofovir alafenamide/emtricitabine [TAF/FTC]). This regimen may be supplied regionally by GSK or reimbursement will be provided as needed.

During the Induction Phase, prior to randomization into the Maintenance Phase at Day 1, one switch to an alternate approved background NRTI therapy is allowed for toxicity or tolerability management. The date of a decision to switch the NRTI background therapy for toxicity or tolerability management must be documented in the electronic case report form (eCRF). Switches of a background NRTI for any other reason are not permitted in the study. Local prescribing information should be consulted for information regarding use of these medications.

For consistency with prescribing information, dose reductions of lamivudine (or emtricitabine if used as alternate NRTI) are permitted as needed for creatinine clearance <50 mL/min (throughout the study). No other dose reductions, modifications, or changes in the frequency of any components of any regimen will be allowed during the Maintenance and Extension Phases of the study.

Following the Induction Phase, in exceptional circumstances, and in consultation with the Medical Monitor, Investigators may provide oral CAB and RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA and who will miss a subsequent scheduled LA injection. 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.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements are essential and required for study conduct.

Study Completion

Participants are considered to have completed the study if they satisfy one of the following:

- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including the Week 100 visit, and did not enter the Extension Phase;

- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including the Week 100 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).

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.

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 201585.

The IDMC will evaluate accumulating efficacy, tolerability and 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/safety/PK 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 ABC/DTG/3TC arm given the partial data set. The sponsor will remain blinded to this analysis.

In addition, the IDMC may also continuously monitor the incidence of participants meeting the confirmed virologic failure 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 into the study is HIV-1 infected antiretroviral (ART) naïve participants.

Assuming a 20% screen failure rate, sufficient ART-naïve participants will be screened (approximately 775) in order to ensure that a total of approximately 620 participants are enrolled at the beginning of the Induction Phase. Assuming 7.5% of enrolled participants will not participate in the Maintenance Phase, this will ensure approximately 570 participants continue into the Maintenance Phase. Participants will be enrolled from multiple sites which may include sites in Canada, France, Germany, Italy, Japan, the Netherlands, Russia, South Africa, Spain, the United Kingdom, and the United States.

Randomization will be stratified by participants' Baseline HIV-1 RNA (<100,000, ≥ 100,000 c/mL) and gender at birth.

A goal of this study is to enroll approximately 20% women, who are typically under-represented in clinical studies. 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.

Participants who prematurely discontinue from the study will not be replaced.

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 participants' Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) and gender at birth. 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 INI STR 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 INI STR 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] – INI STR).

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, 201585, 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.

In descriptive analyses, antiviral response will be assessed according to the proportion of participants with and without oral lead-in who have HIV-1 RNA ≥50 c/mL at Week 124 (i.e., 24 weeks from initiation of CAB LA + RPV LA at Week 100, ±6 week analysis window, using the FDA Snapshot algorithm), with corresponding 95% confidence interval. No formal statistical comparison with respect to safety and efficacy outcomes will be performed.

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

2. INTRODUCTION

Advances in antiretroviral therapies (ART) have led to significant improvements in morbidity and mortality among Human Immunodeficiency Virus (HIV)-infected persons, and has transformed HIV into a chronic manageable disease. Suppression of viral replication is the cornerstone of ART's success and this in turn, is dependent on a participant's ability to adhere to life-long therapy with 3 or more antiretrovirals (ARVs).

Fixed-dose combinations (FDCs) have greatly advanced HIV treatment by allowing simplification of dosing and reducing pill burden. Among regimens of comparable efficacy, physicians and HIV-1-infected participants who receive ART rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Incomplete adherence may lead to the emergence of drug-resistant virus that can lead to the loss of virologic control and reverse the benefits of ART. Different HIV treatment modalities are being developed to help improve adherence and participant outcomes, and prevent the emergence of resistance and transmission of the virus.

There is also an increasing desire to develop nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens that avoid long-term NRTI-associated adverse drug reactions, including renal, hepatic, bone and cardiovascular 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 participants 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), which can also be formulated as a LA product, is a diarylpyrimidine derivative and a 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 profile, as well as improved adherence and treatment satisfaction in virologically suppressed patients.

To date, there are three integrase inhibitors approved in the US and EU for the treatment of HIV-infection: raltegravir (RAL) (Merck), elvitegravir (EVG) (Gilead), and dolutegravir (DTG) (ViiV Healthcare). Two of these three (DTG, EVG) are currently available as components of a once daily single tablet regimen. In April, 2015, the Department of Health and Human Services (DHHS) updated treatment guidelines to include five recommended choices for initial treatment of HIV infection. Four of these five include integrase based therapy as the first line recommended regimen for ART-naïve participants [DHHS, 2015].

DTG is a potent dual cation binding integrase inhibitor, exhibiting rapid reduction in viral load, best in class efficacy, and a high barrier to resistance. DTG is a once daily, unboosted integrase inhibitor that has demonstrated sustained antiviral activity comparable or superior to standard of care in combination with dual NRTIs [Raffi, 2013; Walmsley, 2015]. In addition, due to its mechanism of metabolism, DTG lacks many of the frequent drug interactions associated with other medications commonly taken by HIV-positive patients. To date, the efficacy, PK, safety and drug interaction potential of

DTG has been evaluated in an extensive program of Phase 1 to 3B clinical trials [TIVICAY Prescribing Information, 2017]. DTG has also demonstrated significant improvements over the first marketed INI (RAL), including activity in the presence of integrase (IN)-resistant viruses and an improved dosing regimen (unboosted once daily administration) with similar or improved safety.

Abacavir (ABC)/DTG/lamivudine (3TC) is a combination product of an INI and two NRTIs formulated into a fixed dose combination (FDC) single tablet regimen (STR) that offers the simplicity of a once-daily well-tolerated regimen, with a high genetic barrier for resistance. It may be taken with or without food, and demonstrates few drug-drug interactions in treatment-naïve participants.

The overall objective of this study will be to demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA every 4 weeks compared to continuation of ABC/DTG/3TC over 48 weeks (44 weeks of LA maintenance treatment) in HIV-1 antiretroviral naïve participants.

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 compliance, treatment convenience, and improved quality of life for individuals with HIV compared to current standard of care. 201584 (FLAIR) is being conducted to establish if human immunodeficiency virus type-1 (HIV-1) infected adult participants whose virus is virologically suppressed on an integrase inhibitor single tablet regimen (INI STR), will remain suppressed after 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 a two drug CAB LA + RPV LA regimen every 4 weeks (monthly) compared to remaining on a single tablet integrase based regimen (ABC/DTG/3TC) over 48 weeks. 201584 (FLAIR) will also allow for characterization of long-term antiviral activity, safety, tolerability, and participant satisfaction of the regimens through Week 96.

Additionally, participants initially randomized to continue ABC/DTG/3TC will have an option to switch to CAB LA + RPV LA at, or after, completion of the Week 100 visit. Amendment 04 of the FLAIR study will provide an opportunity to access an *optional* (vs mandatory) oral lead-in for these participants who transition to LA treatment at Week 100. Eligible participants (HIV-1 RNA <50 c/mL at Week 96) would transition to LA dosing, beginning at either Week 100 (direct to injection) or Week 104b (following optional oral lead-in with CAB 30 mg and RPV 25 mg).

Importantly, the oral lead-in during the early development program for CAB LA and RPV LA was instituted to minimize the risk of severe adverse drug reactions during LA dosing (e.g. acute hypersensitivity). The 4 week oral lead-in allowed for an evaluation of any untoward adverse events and an assessment of safety labs prior to initiation of LA therapy. To date, the principal safety risk identified with cabotegravir, following 3145 exposures to drug (oral and/or LA), is suspected DILI, which has occurred in a few

individuals, all of whom were receiving oral CAB. The time to onset ranged between 4 weeks and one year and manifested as asymptomatic elevations of ALT, without compromise to hepatic function. Each participant fully recovered, with removal of investigational product, without hospitalization or intervention. During the Phase 3 ATLAS and FLAIR studies, no cases of DILI have been identified, during the oral lead-in period, or following initiation of LA dosing. There has been no evidence to date of a risk for clinically significant hepatotoxicity observed with cabotegravir. Additionally, throughout the development program to date, no cases of severe drug hypersensitivity or severe drug allergy have been observed. While the risk of idiosyncratic severe drug reactions cannot be fully excluded, the risk of occurrence is felt to be low, on the basis of safety data generated to date.

Based on blinded, instream review of ongoing Phase 3 aggregate AE data (from FLAIR, and ATLAS) and of individual case reports (SAEs), no new, emerging, drug related safety issues have been identified within the four week oral lead-in dosing period (e.g., hypersensitivity, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS], severe drug induced liver injury [DILI]) that would have precluded participants from proceeding to CAB LA + RPV LA injections during the Maintenance Phase of the studies. Additionally, review of accumulating data has not identified any new safety issues occurring on CAB LA + RPV LA that were otherwise predictable based on oral exposure experience.

As a result of the accumulated safety data, which has been generated over the course of the Phase 1, 2 and 3 clinical studies, this amendment has been developed to generate safety, efficacy and PK data for the transition from oral ART to CAB LA + RPV LA without receiving an oral lead-in. These data are intended to inform regulatory discussions around the safe and effective direct to inject dosing option with CAB LA + RPV LA. The decision to dose with or without an oral-lead-in will be optional in this study, as elected by the study participant following informed consent discussions with the investigator.

At Week 124, a descriptive analysis will be conducted to assess antiviral response (HIV-1 RNA ≥50 c/mL) for participants who choose no oral lead-in. No formal statistical comparison will be performed with respect to safety and efficacy outcomes at Week 124.

Data from this optional oral lead in will provide valuable knowledge/insight into the evolution of the ‘direct to injection’ concept.

2.2. Brief Background

- Various approaches to simplify a patient's antiretroviral therapy (ART) regimen, after achieving virologic suppression, have been studied. Previous studies have evaluated switches to ritonavir-boosted PI monotherapy in virologically suppressed participants [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 virologic suppression.

- Other approaches have looked at two nucleoside reverse transcriptase inhibitors (NRTIs) with a ritonavir-boosted protease inhibitor (PI/r) compared to a PI/r + single NRTI. 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. The primary endpoint was the proportion of participants without virologic failure at Week 48. 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 2b studies (LAI116482 [LATTE] and 200056 [LATTE-2]) have been conducted with oral CAB and/or intramuscular (IM) CAB 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) once daily 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 virologic suppression for the CAB groups compared with the EFV group (each p<0·001; log-rank test). A planned Week 48 analysis (24 weeks of CAB + 2 NRTIs Induction, followed by 24 weeks of CAB + RPV Maintenance) demonstrated that 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 participants and 39 (63%) of EFV plus dual NRTI participants 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 regimen consisting of intramuscular (IM) long-acting (LA) CAB LA + RPV LA compared to continuation of oral CAB + ABC / 3TC for the maintenance of HIV-1 RNA suppression. A total of 309 participants were enrolled and treated.

During the Induction Period 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 Period, 286 participants qualified to enter randomization at the Day 1 visit, and were subsequently randomized 2:2:1 onto every 4 week intramuscular (IM) injections with CAB LA + RPV LA (Q4W), every 8 week IM injections with CAB LA + RPV LA (Q8W) 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 data 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, SAEs during the Maintenance Period 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. Based on the data from the Week 48 endpoint, Q4W dosing was chosen to progress for further clinical development.

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 people with living with HIV.

201584 (FLAIR) is being conducted in parallel with study 201585 with the aim to pool data generated from the current study with study 201585, 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 compared to continuation of ABC/DTG/3TC over 48 weeks in HIV-1 antiretroviral naïve participants.	• Proportion of participants with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 48 (Missing, Switch or Discontinuation = Failure, 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 compared to continuation of ABC/DTG/3TC.	• Proportion of participants with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm (Intent-to-Treat Exposed [ITT-E] population). • Proportion of participants with plasma HIV-1 RNA <200 c/mL at Week 48 using the FDA Snapshot algorithm (ITT-E population). • Proportion of participants with plasma HIV-1 RNA <200 c/mL and HIV-1 RNA <50 c/mL at Week 96 using the FDA Snapshot algorithm (ITT-E population). • Proportion of participants with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 96. • Proportion of participants with confirmed virologic failure at Week 48 and Week 96. • Absolute values and change from Baseline in plasma HIV-1 RNA at Week 48 and Week 96. • Absolute values and changes from Baseline in CD4+ cell counts over time including Week 48 and Week 96. • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death).
To evaluate the safety and tolerability of switching to CAB LA + RPV LA every 4 weeks compared to continuation of ABC/DTG/3TC over time.	• Incidence and severity of AEs and laboratory abnormalities over time including Week 48 and Week 96. • Proportion of participants who discontinue treatment due to AEs over time including Week 48 and Week 96.

Objectives	Endpoints
	• Absolute values and changes in laboratory parameters over time including Week 48 and Week 96.
To evaluate the effects of CAB LA + RPV LA every 4 weeks on fasting lipids over time compared to continuation of ABC/DTG/3TC over time.	• Change from Baseline in fasting lipids over time including Week 48 and Week 96.
To assess the development of 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 and Week 96.
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 assess the acceptance of pain and injection site reactions following injections.	• 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).
To assess degree of health-related quality of life (HR QoL).	• 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 treatment satisfaction of CAB LA +	• Change from baseline in total “treatment

Objectives	Endpoints
RPV LA compared to continuation of ABC/DTG/3TC.	satisfaction" score, and individual item scores of the HIV Treatment Satisfaction Questionnaire (status version) (HIVTSQs) at Week 4b, Week 24, Week 44, Week 96 (or Withdrawal). • Change in treatment satisfaction over time (using the HIVTSQ change version [HIVTSQc]) at Week 48 (or Withdrawal).
To assess 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 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 injections at Week 5, Week 40, Week 41, and Week 96 using the Numeric Rating Scale (NRS) within the CAB LA + RPV LA arm.
To evaluate the antiviral and immunologic effects, safety and tolerability, and viral resistance of CAB LA + RPV LA at Week 124 and over time for participants switching from ABC/DTG/3TC in the Extension Phase, *with and without oral lead-in.*	• Proportion of participants with HIV-1 RNA $\geq$ 50 c/mL at Week 124, with and without oral lead-in (FDA Snapshot algorithm, Extension Switch population). • Proportion of participants with plasma HIV-1 RNA <50 c/mL and HIV-1 RNA <200 c/mL over time. • Proportion of participants with confirmed virologic failure over time. • Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV over time. • Absolute values and change from Baseline in CD4+ cell counts over time. • Incidence and severity of AEs and laboratory abnormalities over time. • Proportion of participants who discontinue

Objectives	Endpoints
	treatment due to AEs over time. • Absolute values and change in laboratory parameters over time.
To evaluate the pharmacokinetics of CAB and RPV in the setting of no oral lead-in for participants switching from ABC/DTG/3TC in the Extension Phase.	• To evaluate plasma CAB and RPV concentrations over time (Week 100 [direct to inject without oral lead-in] and Week 104 [both direct to inject and optional oral lead-in participants])
Exploratory	
To explore the effect of participant characteristics on the virologic and immunologic response of CAB LA and RPV LA compared to continuation of ABC/DTG/3TC.	• 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, and 96 using the Snapshot algorithm for the ITT-E population. • Proportion of participants by subgroup(s) (e.g. by age, gender, BMI, race, HIV-1 subtype, Baseline CD4+) with plasma HIV-1 RNA <50 c/mL at Week 48 and Week 96. • Change from Baseline in CD4+ cell counts by subgroups at Week 48 and Week 96.
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 receiving CAB LA and RPV LA compared to continuation of ABC/DTG/3TC over time.	• Absolute values and change from Baseline in renal (in urine and blood) and bone (in blood) biomarkers over time including Week 48 and Week 96.
To assess preference for CAB LA + RPV LA compared to oral antiretroviral (ARV) therapy using a single dichotomous preference question.	• For participants randomized to the "CAB LA + RPV LA" arm, preference for CAB LA + RPV LA compared to oral ARV regimen, at Week 48.

4. STUDY DESIGN

4.1. Overall Design

201584 (FLAIR) is a 120-week Phase 3, multi-phase, randomized, open label, active-controlled, multicenter, parallel-group, non-inferiority study in HIV-1, ART-naïve adult participants. Participants who fulfill eligibility requirements will enroll into the Induction

Phase of the study and receive ABC/DTG/3TC for 20 weeks (Week [-20] to Day 1). Participants who have an HIV-1 RNA <50 c/mL at Week (-4) will be randomized (1:1) into the Maintenance Phase at Day 1 to either continue ABC/DTG/3TC or to discontinue ABC/DTG/3TC 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). ABC/DTG/3TC dosing on Day 1 should 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 ABC/DTG/3TC prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1. Participants who are not eligible to continue into the Maintenance Phase will be withdrawn from the study. At the Week 4a visit, assessments (including e.g. clinical chemistries) will be performed as per the Time and Events Table (Table 5). At the Week 4b visit, 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 4b visit can be performed as soon as central laboratory results become 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 period 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. The second and third IM injections (CAB LA 400 mg + 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 injections occur within the window of Week 7 to Week 8, but not later than Week 8), and the third injections occur within the window of Week 11 to Week 12, but no later than Week 12. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, with a ± 7 day dosing window being allowed (but not preferred). In addition, starting at the Week 12 injection (third injection), the interval between injection visits should be limited to a maximum of 5 weeks. If the length of time between injections exceeds, or is projected to exceed 5 weeks, the Medical Monitor must be contacted to discuss individual participant case management.

Participants randomized to ABC/DTG/3TC during the Maintenance Phase will continue ABC/DTG/3TC for at least an additional 100 weeks. Participants who successfully complete Week 100 (without meeting study defined withdrawal criteria and who remain virologically suppressed through Week 96: 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. The transition from ABC/DTG/3TC to CAB LA + RPV LA within the Extension Phase can be completed with or without an oral lead-in prior to commencement of injectable treatment. The oral lead-in decision will be made by the participant in consultation with the investigator and must be appropriately documented.

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 will enter a 52 week Long-Term Follow-Up Phase. Participants must remain on suppressive highly active

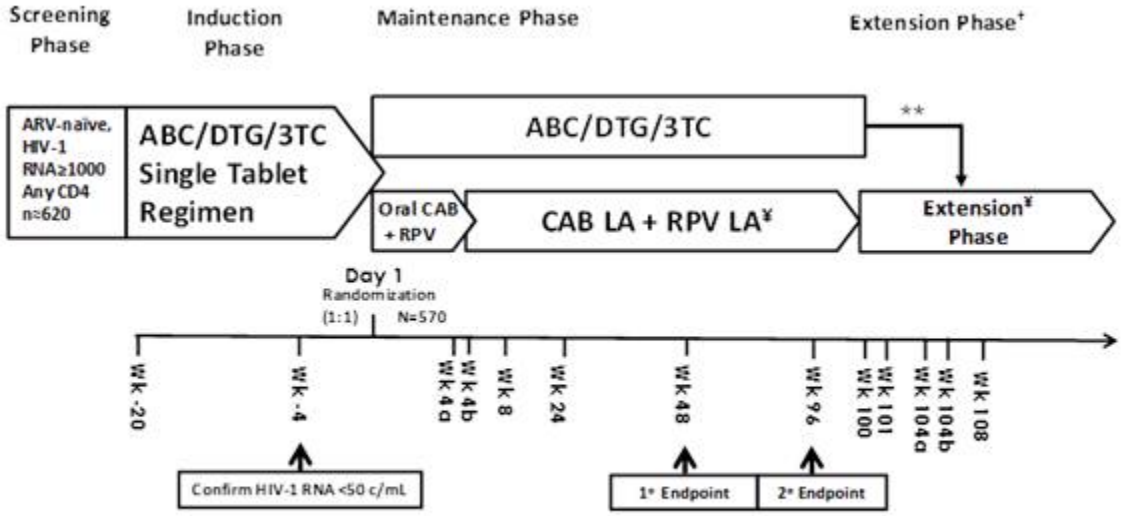
antiretroviral therapy (HAART) for at least 52 weeks after the last dose of CAB LA and/or RPV LA.

In order to achieve balance across the two treatment arms, randomization will be stratified by participant's Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) and gender at birth. The primary endpoints for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 (48 weeks of two drug maintenance treatment, 44 weeks of LA therapy). 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 comparison.

Approximately 620 subjects will be enrolled into the Induction Phase of the study. Assuming 7.5% of enrolled participants will not participate in the Maintenance Phase, this will ensure approximately 570 participants continue into the Maintenance Phase. The sample size of 285 per arm (at Day 1 randomization) is such that the study has approximately 97% power to demonstrate non-inferiority in the proportion of participants with snaphot virologic failure at Week 48 using an 6% margin, assuming a true 3% failure rate for CAB and a 2% failure rate for the ABC/DTG/3TC control arm and using a 2.5% one-sided alpha level.

An Independent Data Monitoring Committee (IDMC) will evaluate interim efficacy, tolerability and 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. 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 LA + RPV LA arm. Additional details are provided in Section 9.3.3, and in the IDMC charter, which is available upon request.

Figure 1 201584 (FLAIR) Study Schematic



** Optional oral lead-in (investigator discretion) available from Week 100 to Week 104b

¥Subjects who withdraw from IM CAB LA + RPV LA must enter the 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.

All participants will complete the Screening phase of up to 35 days prior to Baseline (Week [-20]) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. All Screening results **must** be available prior to enrolment. 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. Similarly, if a central laboratory result cannot be generated for genotype/phenotype, a local result can be considered following review and approval by the study virologist.

Participants not meeting all inclusion and exclusion criteria at initial screen may be re-screened one time with a new participant number. Participants who are enrolled into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be enrolled as soon as all eligibility requirements have been confirmed at the site.

4.2.2. Induction Phase

Following the Screening Phase, eligible participants will be enrolled into the study and begin a 20 week Induction Phase study on ABC/DTG/3TC (Week [-20] to Day 1). ABC/DTG/3TC dosing on Day 1 should 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 ABC/DTG/3TC prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned on Day 1.

4.2.3. Eligibility for the Maintenance Phase

Participants with an undetectable HIV-1 RNA (<50 c/mL) at the Week (-4) visit are eligible to enter the Maintenance Phase. A single repeat HIV-1 RNA test to determine eligibility may be allowed ONLY after consultation with the medical monitor. Participants with HIV-1 RNA ≥400 c/mL at Week (-4) are not eligible to enter the Maintenance Phase, will not be allowed a repeat to determine eligibility, and will therefore be withdrawn from the study.

Result of HIV-1 RNA at Week (-4)	**Action**
<50 c/mL	Begin Maintenance Phase at Day 1.
≥50 c/mL but <400 c/mL	Single repeat allowed only after consultation and approval from Medical Monitor.
Single repeat <50 c/mL	Begin Maintenance Phase at Day 1.
Single repeat ≥50 c/mL	Cannot begin Maintenance Phase and must be withdrawn from study; Complete withdrawal visit instead of Day 1.
≥400 c/mL	Cannot begin Maintenance Phase and must be withdrawn from study; Complete withdrawal visit instead of Day 1.

Should a participant be allowed a repeat, results of this repeat must be available prior to Day 1, therefore the time needed for scheduling the visit, lab draws and lab analysis should be considered.

The Medical Monitor may advise the site to withdraw a participant from the study prior to Week (-4) if the participant is unlikely to be eligible for the Maintenance Phase.

Participants ineligible for the Maintenance Phase will be withdrawn.

If the participant is ineligible for the Maintenance Phase, samples with a HIV-1 RNA >400 c/mL will be sent to a central laboratory for resistance testing and results provided to the Investigator once available.

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 Maintenance Phase.

4.2.4. Maintenance Phase (Day 1 to Week 100)

At Day 1, the Maintenance Phase begins. 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 (Section 7.1.), including clinical chemistries. At the Week 4b visit, 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 Week 4b visit can be performed as soon as central laboratory results from the Week 4a visit become 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 period 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. The second and third IM injections (CAB LA 400 mg + 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 injections occur within the window of Week 7 to Week 8, but not later than Week 8), and the third injections occur within the window of Week 11 to Week 12, but no later than Week 12. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks (monthly) thereafter, with a ± 7 day dosing window being allowed (but not preferred). In addition, following the Week 12 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. The dosing window (±7 days) for injections after Week 12 is allowed, but also not preferred.

  OR

- Continue on oral ABC/DTG/3TC initiated during the Induction Phase for at least an additional 100 weeks. Participants who successfully complete Week 100 (without meeting study defined withdrawal criteria and who remain virologically suppressed through Week 96: 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.
- ABC/DTG/3TC dosing on Day 1 should 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 ABC/DTG/3TC prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned on Day 1.

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 between Day 1 and Week 4b, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA** (See Section 7.4.5.13).

Participant randomization will be stratified by participants' Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) and gender at birth.

4.2.5. Extension Phase

All eligible participants who transition into the Extension Phase 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.

Participants not eligible to enter the Extension Phase will end their study participation (Week 100 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.

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

All participants who successfully complete 100 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. See the Time and Events Table (Section 7.1) for more information.

4.2.5.2. Participants Entering from the ABC/DTG/3TC Arm

Participants randomized to continue ABC/DTG/3TC 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 100 (no withdrawal visit needed). The transition from ABC/DTG/3TC to CAB LA + RPV LA within the Extension Phase can be completed with or without an oral lead-in prior to commencement of injectable treatment. The participant's decision will be taken in consultation with the investigator and must be appropriately documented. As participants approach the Week 100 visit, sites must ensure sufficient CAB and RPV supply are available to support the participant's decision for transition to LA.

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 ABC/DTG/3TC while eligibility is being confirmed.

All participants with an undetectable HIV-1 RNA (<50 c/mL) result from the Week 96 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 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 with a 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 96 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.

Result of HIV-1 RNA at Week 96	**Action**
<50 c/mL	Begin Extension Phase at Week 100
≥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 at Week 100
Single repeat ≥50 c/mL	Cannot begin Extension Phase and must be withdrawn from study; Complete Week 100 visit (no withdrawal visit required)
≥400 c/mL	Cannot begin Extension Phase and must be withdrawn from study; Complete Week 100 visit (no withdrawal visit required)

Participants Transitioning Direct to Injection in the Extension Phase:

Central lab results and safety parameters from the Week 96 visit must be available and reviewed for participants who choose to transition directly to injections. Participants with ongoing safety issues or laboratory abnormalities of clinical concern (e.g. Grade 3 or Grade 4 liver chemistry elevations) will require consultation and agreement with the Medical Monitor prior to proceeding directly to injections in the Extension Phase.

If a clinical chemistry retest is required based on Week 96 labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 96). Participants will remain on oral ABC/DTG/3TC until the Week 100 injection visit, and until any required Week 96 retest results are available for review.

At Week 100, eligible participants will take the last dose of ABC/DTG/3TC (or DTG + 2 NRTIs), and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg) as initial loading doses. Clinical chemistries will also be assessed at Week 100. At Week 101, participants will return to the clinic for PK and safety assessments including clinical chemistries. The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104a and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104a, but not later than Week 104a, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 108 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 Receiving Optional Oral Lead-In in the Extension Phase:

As participants approach the Week 100 visit, sites must ensure sufficient oral CAB and RPV are available for participants who choose to use the oral lead-in.

At Week 100, eligible participants who after discussion with the investigator, choose to receive the optional oral lead-in will initiate a 4 week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily. It is not necessary to dose ABC/DTG/3TC on the day the participant begins the oral lead-in with CAB + RPV. However, if the participant takes ABC/DTG/3TC prior to coming into the clinic, initiation of oral CAB and RPV should continue as planned. Clinical chemistries will be assessed at Week 100. At Week 104a, 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 104a visit must be available and reviewed before the Week 104b visit. If a clinical chemistry retest is required based on Week 104a labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 104a). Participants will remain on oral CAB 30 mg + RPV 25 mg until the Week 104b injection visit, and until any required Visit 104a retest results are available for review.

At Week 104b visit, 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 Week 104b visit can be performed as soon as central lab results from the Week 104a visit become available and safety parameters are reviewed. The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 108 and Week 112. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 107 to Week 108, but not later than Week 108, and the third injections occur within the window of Week 111 to Week 112, but no later than Week 112. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks (monthly) thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 112 injection, the interval between injection visits should be limited to a maximum of 5 weeks. If the length of time between injections exceeds, or is projected to exceed 5 weeks, the Medical Monitor must be contacted to discuss individual participant case management.

4.2.6. 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 highly active antiretroviral therapy (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 four weeks of the last injection.

- The 52 weeks follow up phase will begin the day of the last CAB LA and/or RPV LA dose. 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 Table (Section 7.1.).

- Participants will be assessed with clinic visits at Months 1, 3, 6, 9 and 12. Female participants of child bearing potential must continue to use adequate contraception methods 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 participating in the Long-Term Follow-Up Phase. The participants' last on study visit will be considered the withdrawal visit.

4.2.7. Dose Modifications / Permitted Treatment Substitutions

Participants who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on DTG and an approved dual-NRTI backbone that does not contain abacavir (e.g. tenofovir/emtricitabine [TDF/FTC] or tenofovir alafenamide/emtricitabine [TAF/FTC]). This regimen may be supplied regionally by GSK or reimbursement will be provided as needed.

During the Induction Phase, prior to randomization into the Maintenance Phase at Day 1, one switch to an alternate approved background NRTI therapy is allowed for toxicity or tolerability management. The date of a decision to switch the NRTI background therapy for toxicity or tolerability management must be documented in the eCRF. Switches of a background NRTI for any other reason are not permitted in the study. Local prescribing information should be consulted for information regarding use of these medications.

A short term bridging supply for participants on the CAB LA + RPV LA arm may be permitted following discussion with the Medical Monitor (see Section 6.8.1).

For consistency with prescribing information, dose reductions of lamivudine (or emtricitabine if used as alternate NRTI) are permitted in the context of renal insufficiency (throughout the study), e.g. as needed for creatinine clearance <50 mL/min.

If a dose reduction of lamivudine, a component of TRIUMEQ, is required for participants with creatinine clearance less than 50 mL/min, the individual entities should be used (e.g. DTG tablets, ABC tablets, 3TC tablets as separate medications, with dosing consistent with prescribing information). DTG can be provided centrally through the study. Single entity products will need to be sourced locally and can be reimbursed by the Sponsor as needed. Lamivudine (3TC) dose reduction will be allowed throughout the study, and is not considered to be a "switch to an alternative approved background NRTI therapy", but rather an alignment with prescribing information to maintain consistent 3TC plasma exposure for participants with renal insufficiency.

No other dose reductions, modifications, or changes in the frequency of any components of any regimen will be allowed during the Maintenance and Extension Phases of the study.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements are essential and required for study conduct.

4.2.8. 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 (201584) and study 201585.

An IDMC will evaluate accumulating efficacy, tolerability / safety, and PK of CAB LA + RPV LA at predetermined times during the study. 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 ABC/DTG/3TC 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 criteria through Week 48 to ensure that participants are not being sub-optimally treated in the CAB + RPV arm.

Additional ad hoc analyses may be scheduled if needed.

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.

4.3. Type and Number of Participants

Assuming a 20% screen failure rate, sufficient ART-naïve participants will be screened (approximately 775) in order to ensure that a total of approximately 620 participants are enrolled at the beginning of the Induction Phase. Assuming 7.5% of enrolled participants will not participate in the Maintenance Phase (based on the rate of withdrawals observed during the Induction Period of study 200056), 620 participants enrolled into the Induction

Phase will ensure approximately 570 participants continue into the Maintenance Phase. Participants will be enrolled from multiple sites which may include sites in Canada, France, Germany, Italy, Japan, the Netherlands, Russia, South Africa, Spain, the UK, and the US.

Randomization will be stratified by participants' Baseline HIV-1 RNA (<100,000, ≥ 100,000 c/mL) and gender at birth.

A goal of this study is to enroll approximately 20% women who are typically under-represented in clinical studies. 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 key study populations.

Participants who prematurely discontinue from the study will not be replaced.

4.4. 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 with virologic failure per Snapshot algorithm at Week 48 is the FDA recommended endpoint for switch design studies (Center for Drug Evaluation and Research, Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment, 2015).

- Various approaches to simplify a participant's antiretroviral therapy (ART) regimen, after achieving virologic suppression, have been studied. Previous studies have evaluated switches to ritonavir-boosted PI monotherapy therapy in virologically suppressed participants [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 virologic suppression.

In addition, the 200056 (LATTE-2) clinical trial, evaluated a different simplification approach and served as proof of concept for 201584 (FLAIR). In 200056, HIV-1 RNA suppression was induced with a three drug antiretroviral regimen consisting of CAB + ABC/3TC FDC, and then participants transitioned to a two-drug two-class regimen consisting of CAB LA + RPV LA for the maintenance of HIV-1 RNA suppression. 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. During the Maintenance Period, there was one protocol confirmed virologic failure (CVF) on Q8W dosing and one CVF on oral dosing, without any evolution of resistance. The CVF on Q8W dosing occurred

following an aberrant RPV injection, without measurable RPV concentrations 4 weeks post dosing. Overall AEs and clinical chemistries, were in line with 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 32 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 Week 48 data demonstrated similar virologic success between the Q4W and Q8W arms, with 92% (Q8W) and 91% of participants remaining suppressed (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, there were more Snapshot failures for virologic reasons on the Q8W arm (7%) compared to the Q4W arm (<1%), and more participants with Snapshot failure for non-virologic reasons (discontinued due to AE or other reasons) on the Q4W arm (8%) compared to the Q8W arm (<1%). Additionally, between Week 32 and Week 48, one additional participant (Q8W) had confirmed virologic failure, with treatment emergent NNRTI (K103N, E138G, and E238T) and integrase (Q148R). See Section 2 for additional information on this participant.

On the basis of these 200056 data, Q4W dosing was selected to progress into Phase 3 for further clinical development.

The open-label design for 201584 (FLAIR) best suits the objectives of this study. A double-blind, double-dummy design for this study would result in an increased pill burden in all participants, a requirement for placebo injections across the comparator arms, elevated risk of oral ART non-adherence in participants receiving placebo injections, limitations to patient reported preference data comparing injectable and oral ART, as well as considerable trial design complexities.

A blinded design is also complicated by the requirement for an oral lead-in, in the CAB LA + RPV LA arm only. Blinding the oral lead-in would require additional placebo pills for 5 weeks in the ART continuation arm, that otherwise would not be required.

In addition to study design challenges, the impact of blinding in both studies carries the potential risk of oral regimen non-compliance, in participants on the ART continuation arm, who may believe that they are receiving active drug via injection (and therefore possibly increased risk of HIV 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 studies are planned as open label studies.

4.5. Dose Justification

4.5.1. 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 LATTE and 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 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 2b, 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 compared to efavirenz (EFV) 600 mg once daily with two NRTIs. 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 2b 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 LAI116482: Proportion (95% CI) of Participants with Plasma HIV-1 RNA <50 c/mL at Key Visits- Snapshot (MSDF) Analysis (ITT-E Population)

Visit		CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	CAB Subtotal N=181	EFV 600 mg
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 two NRTIs during the 24 week Induction Period.
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 4.5.2, 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.

The oral lead-in for participants randomized to the ABC/DTG/3TC arm who choose to receive CAB LA + RPV LA during the Extension Phase of the study is optional. Without oral lead-in dosing, CAB LA and RPV LA achieve concentrations following their initial injections similar to induction doses of their respective efficacious oral products. Oral ABC/DTG/3TC administered up to and including the day of the initial CAB LA + RPV LA injections will provide additional exposure to active antiviral agents during the

transition from oral to LA treatment (e.g., exposure that would replace oral CAB + RPV exposure).

4.5.2. 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 every 4 week 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 4.5.1, 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 Period (16 weeks of oral CAB + 2 NRTIs, 4 weeks of CAB + 2 NRTIs + oral RPV). Subjects who were eligible to continue into the Maintenance Period 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 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 Week 48, 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 subjects 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 subject, randomized to the Q8W regimen and one subject 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 LATTE-2: Proportion (95% CI) of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 - Snapshot (MSDF) Analysis (ITT-E Population)

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 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, 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 CAB PK Parameters following Repeat Dose Administration of Cabotegravir LA to HIV-infected Subjects (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(Week 40 to Week 44) for Q4W (n=80) and AUC(Week 40 to Week 48) for Q8W regimen (n=93).

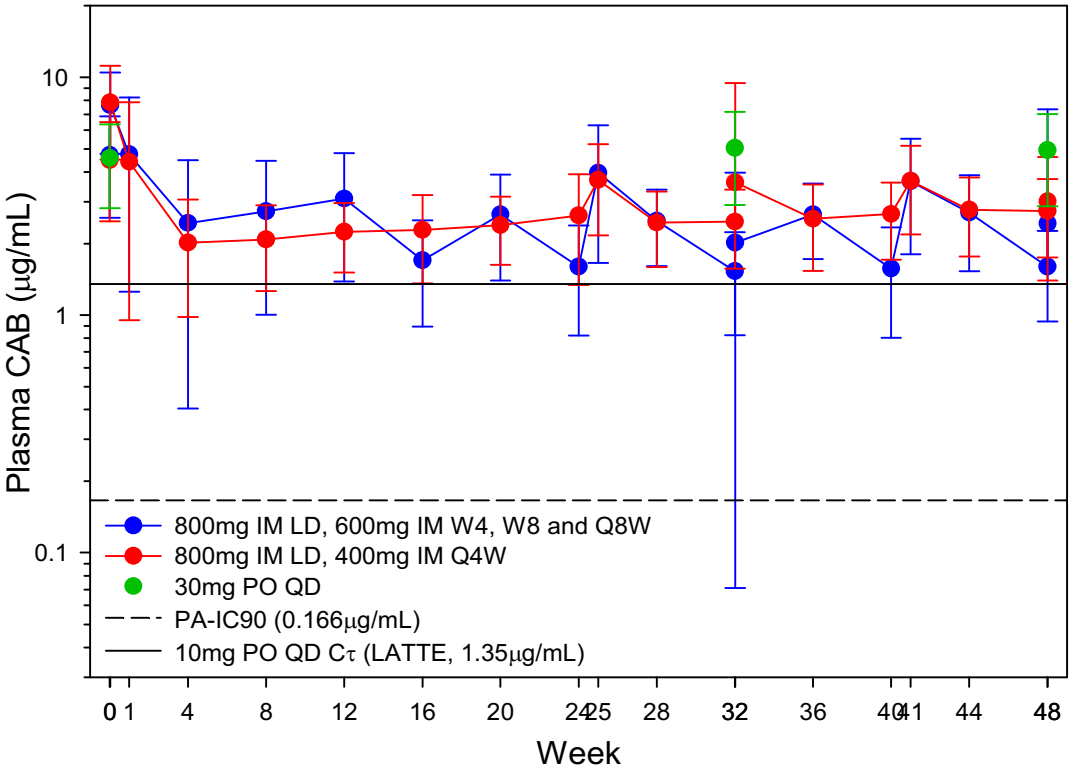
c. Cmax: Q4W: between Week 24 and Week 28 (n=97) or Week 40 and Week 44 (n=95); Q8W: between Week 24 to Week 32 (n=98) or Week 40 and Week 48 (n=104).

d. Individual Average C0 Week 24 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 Week 40 using troughs at Week 40, Week 44, and Week 48 for Q4W (n=98) and Week 16, Week 24, Week 32, Week 40 and Week 48 for Q8W (n=112).

e. Tmax presented as median (range) in days, (Week 24 to Week 32: n=97 Q4W arm, n=98, Q8W arm; Week 40 to Week 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 CAB 30 mg 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 RPV LA to HIV-infected Subjects (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%]

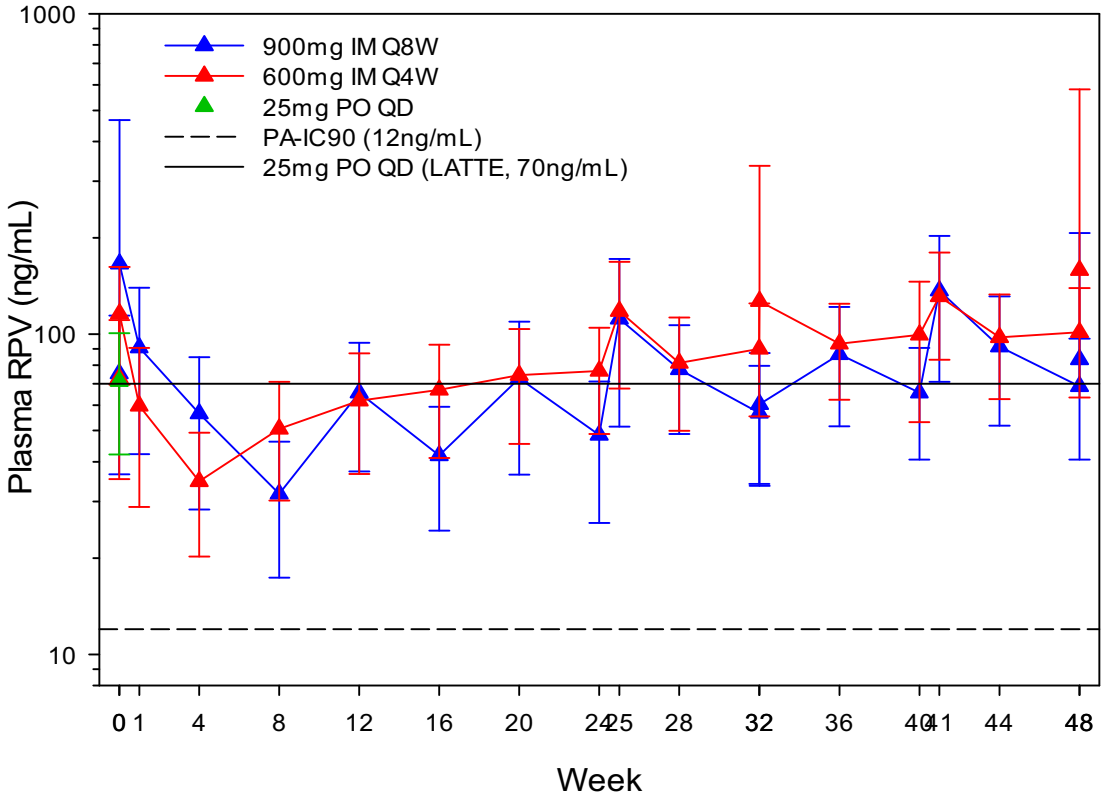
b. AUC(0-τ) = AUC(Week 24 to Week 28) for Q4W regimen (n=84), and AUC(Week 24 to Week 32) for Q8W regimen (n=86) or AUC(Week40 to Week 44) for Q4W (n=80) and AUC(Week 40 to Week 48) for Q8W regimen (n=92) via non-compartmental PK analysis

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 Week 24 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 Week 40 using troughs at Week 36, Week 40, Week 44, and Week 48 for Q4W (n=102) and Week 40 and Week 48 for Q8W (n=100)

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

Figure 3 Mean (SD) Observed Concentration-Time Data following RPV LA Q8W and Q4W and Cτ (following RPV 25 mg Oral Once Daily[a]) through Week 48 (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 have been optimized for the present study. In LATTE-2, the Q4W dosing regimen for CAB LA included a 1st dose of 800 mg (two 2 mL 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 600 mg 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 600 mg 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 Q4W thereafter = Study Week 4b, Week 8, and Q4W thereafter, respectively.

In summary, a modified Q4W 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 3 mL each, at doses of 600 mg and 900 mg, respectively. Subsequent injections of CAB LA and RPV LA will be 2 mL each, at doses of 400 mg and 600 mg, respectively (see also Section 4.5.3).

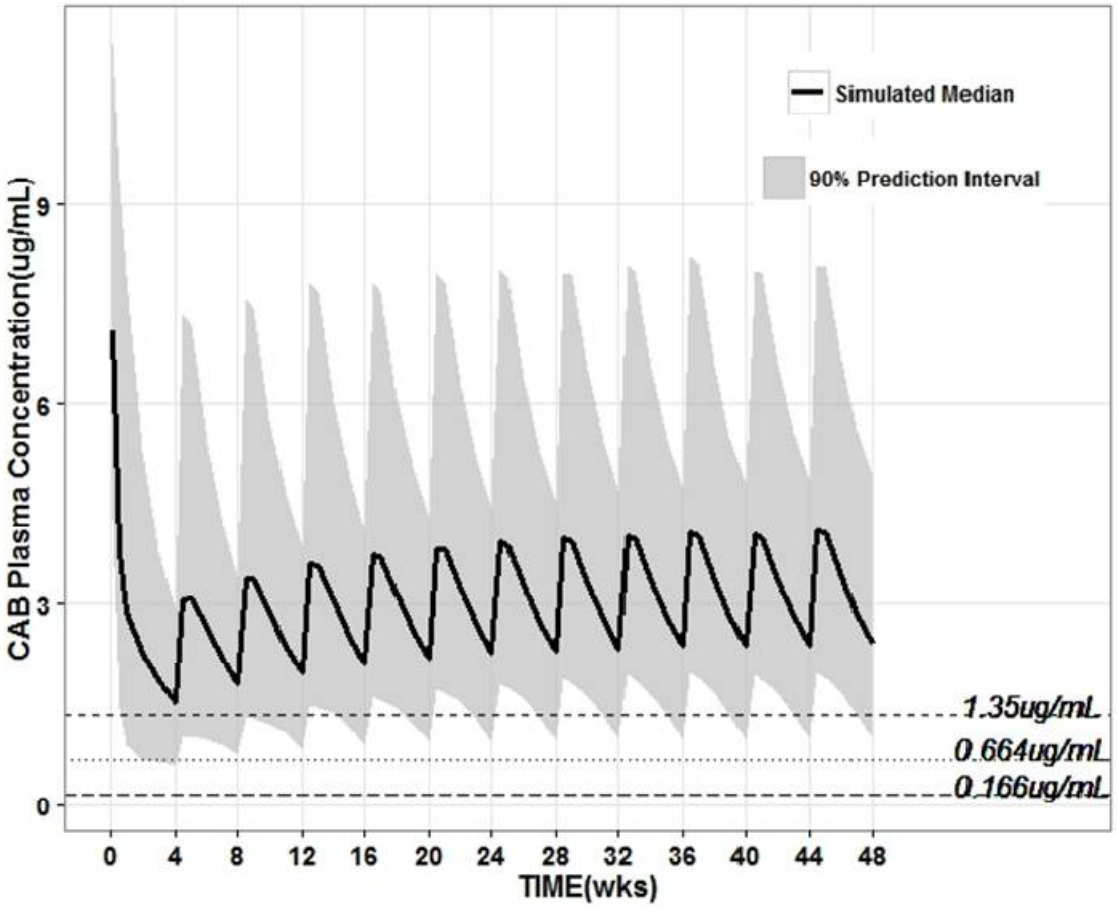
4.5.3. Modeling and Dose Simulations for CAB LA and RPV LA

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.

4.5.3.1. CAB LA

For CAB LA, the model included data from 416 subjects who received CAB LA as single or repeat administration, with approximately 50% of data obtained from 200056 (LATTE-2), approximately 20% from 201120 (CAB LA PrEP study), and approximately 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 PA-IC90, and 88% is predicted to achieve trough concentrations above the geometric mean trough following the 10 mg oral dose in LATTE of 1.35 μg/mL (8x PA-IC90).

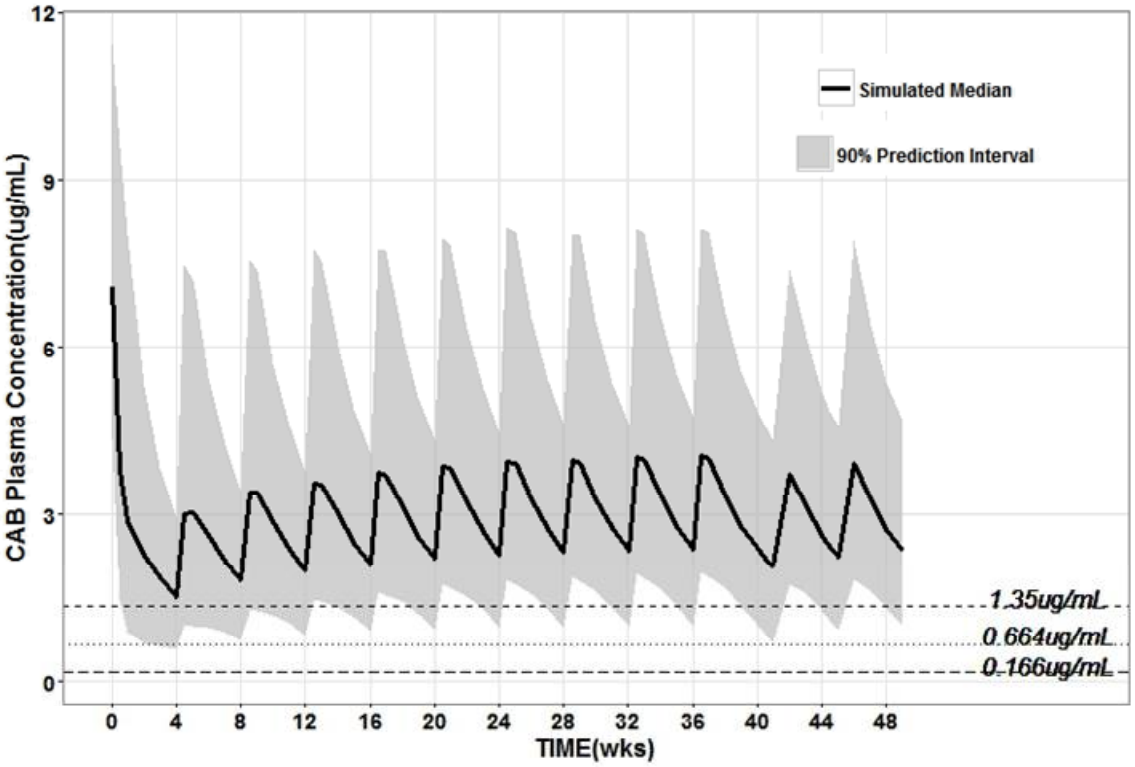
Figure 4 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the CAB LA Q4W Regimen (600 mg IM Day 1, then 400 mg IM Q4W thereafter^)



* 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)
Medium dashed line at 1.35 μg/mL corresponds to the geometric mean Ctrough concentration following oral CAB 10 mg once daily (LATTE) and is equivalent to 8x PA-IC90
Dotted line at 0.664 μg/mL corresponds to 4x PA-IC90
Long dashed line at 0.166 μg/mL corresponds to the PA-IC90.

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

Figure 5 Impact of 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 (600 mg IM Day 1, then 400 mg IM Q4W thereafter^)



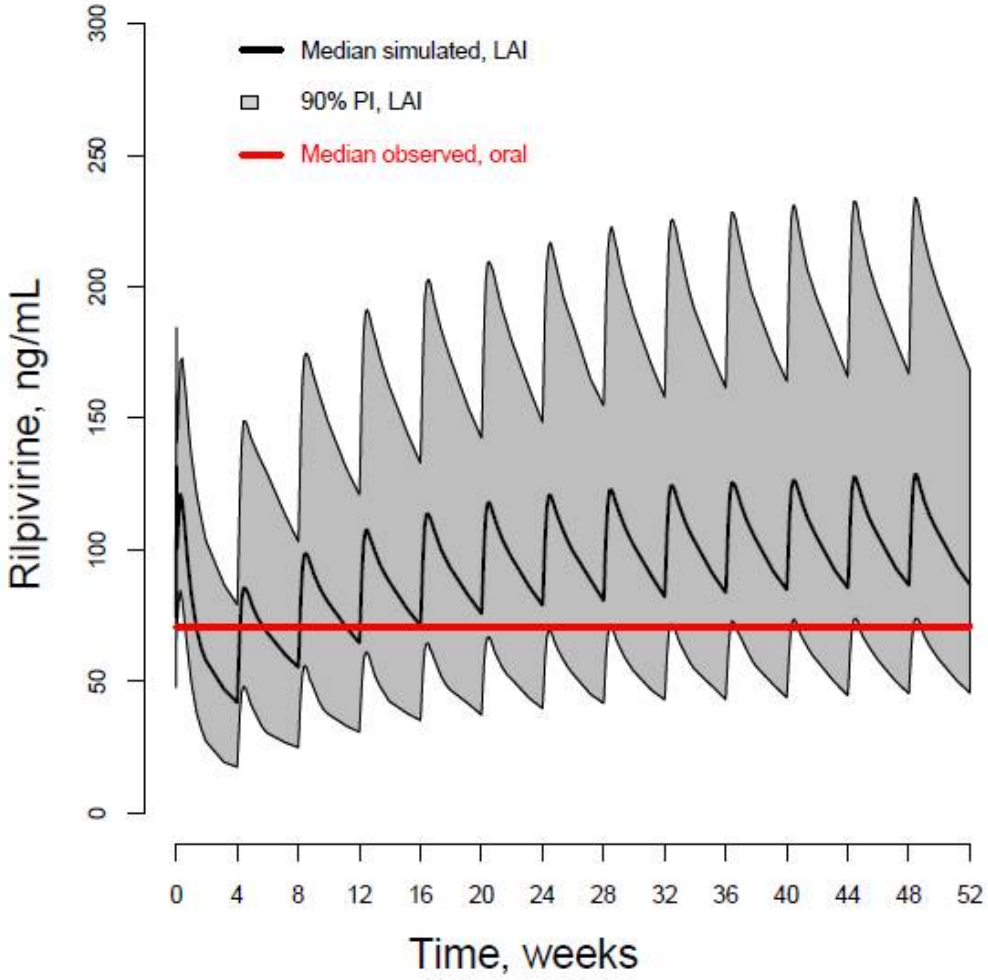
* Note: current simulations based on interim plasma concentration dataset
^Study Time and Events include a 4 week oral lead in. Therefore, Day 1 = day of first injections (Week 4b study visit); Week 4 = second injections (Week 8 study visit)
Medium dashed line at 1.35 μg/mL corresponds to the geometric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

4.5.3.2. 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.

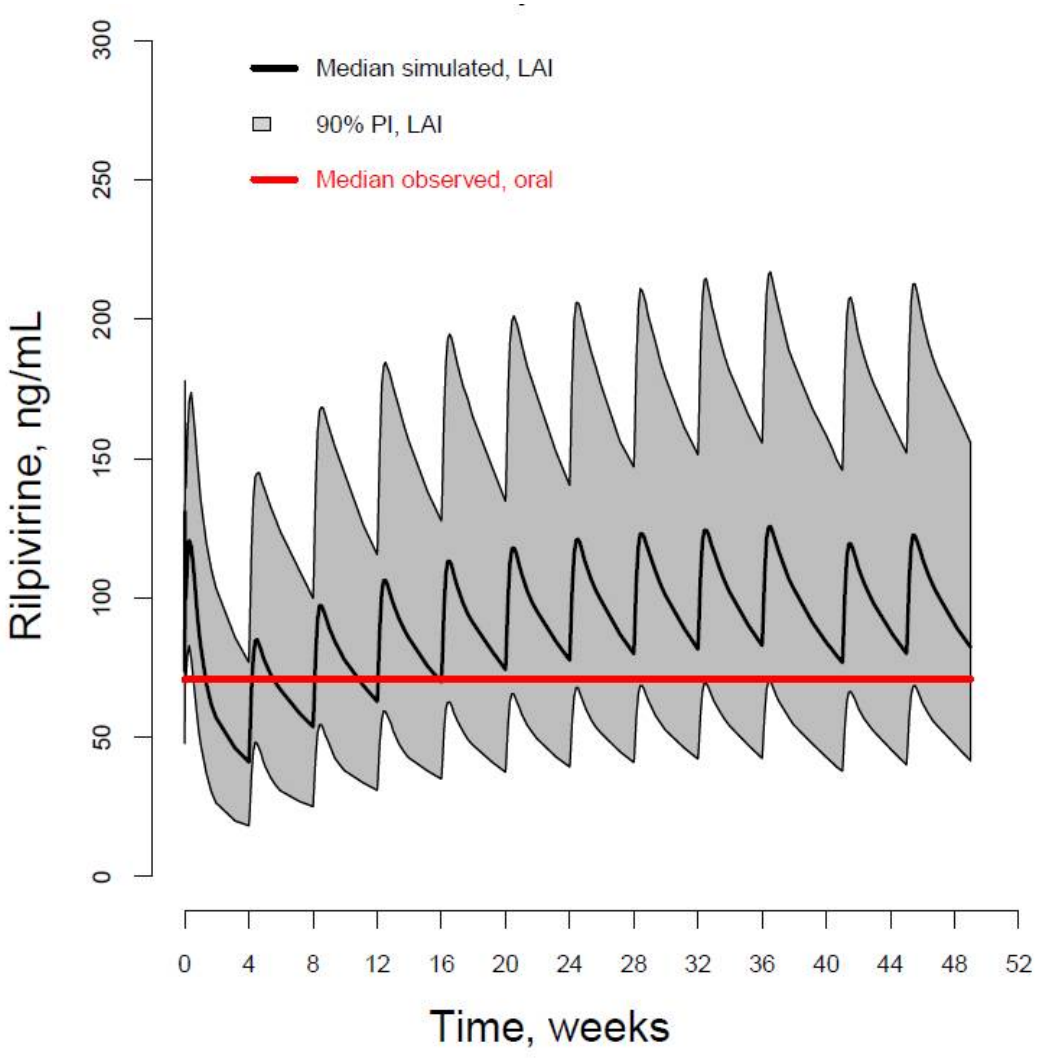
Figure 6 **Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the RPV LA Q4W regimen (900 mg IM Day 1, then 600 mg IM Q4W thereafter^)**



* 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 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)

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 25 mg (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 Cτ following oral RPV 25 mg 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)

4.6. 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 Brochures (GlaxoSmithKline Document Number RH2009/00003/07; 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 Prescribing Information, 2018).

ABC/DTG/3TC is an established regimen that has been in clinical use for several years and has an established benefit/risk profile described in detail in the DTG IB (GlaxoSmithKline Document Number RM2007/00683/11) and respective country product labels (TRIUMEQ Prescribing Information, 2018).

A potential safety issue related to neural tube defects in infants born to women with exposure to dolutegravir (DTG) at the time of conception has been recently identified as noted below:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [ABC/DTG/3TC, DTG] Refer to DTG IB and country product labels for additional information		
DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, 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) from 30 days prior to the first dose of study medication 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. 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded; 3. Women who become pregnant, or who desire to be pregnant while in the study will have study treatment discontinued and withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR). 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 participants, 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., TRIUMEQ, ZIAGEN, EPZICOM / KIVEXA or TRIZIVIR) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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 TRIUMEQ (or EPZICOM if TRIUMEQ is not available within country).

Mitigation for ABC HSR: Every potential participant will be screened for the carriage of the *HLA-B*5701* allele. Participants who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on a dual-NRTI backbone that does not contain abacavir (see Section 6.8).

The following section outlines the risk assessment and mitigation strategy for CAB and RPV in this protocol.

4.6.1. 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	A small proportion of participants in the CAB program to date (total exposure >3100 participants) have developed transaminitis (elevated liver transaminases characterised by predominant ALT elevation). In some of these participants' transient transaminitis were explained by acute hepatitis C infection and whilst a small number of others did not have alternative explanations, suggesting a mild form of DILI without hepatic dysfunction which resolved upon withdrawal of treatment with CAB. Of the four participants with possible or probable cases of DILI identified in Phase 2 studies, all were receiving oral CAB.	• Exclusion criteria as described in Section 5.2 will prohibit participants with significant liver impairment based on screening liver chemistry including transaminases (ALT and 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 period was implemented at the beginning of this study, where all participants will receive oral CAB prior to the administration of CAB LA to determine individual safety and tolerability. During the Extension Phase of the study, following review of available oral lead-in and Maintenance Phase safety data, the protocol was amended to allow an optional oral lead-in for the participants transitioning from

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		ABC/DTG/3TC to CAB LA+RPV LA. • 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 7.4.5.1 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 ULN while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA. • All instances of liver transaminase elevations of Grade 2 and above will be followed to resolution. Participants withdrawn from CAB treatment due to meeting liver chemistry stopping criteria will be regularly monitored both clinically and using liver chemistries to determine progress towards resolution of the liver event.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 receiving multiple injections. Although some Grade 3 ISRs were reported, the majority of ISRs 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 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 will be given 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. • Specialist dermatology consultation will be sought if warranted for individual participants.
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,	• The risk of developing a hypersensitivity reaction post administration of CAB LA was minimized at the start of the study by the use of a mandatory 4-week oral lead-in of CAB to determine individual safety and tolerability

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 CAB LA. The long exposures anticipated after CAB LA injection may complicate the management of a drug hypersensitivity reaction, were it to occur.	prior to the introduction of CAB LA. During the Extension Phase of the study, following review of available oral lead-in and Maintenance Phase safety data, the protocol was amended to allow an optional oral lead-in for the participants transitioning from ABC/DTG/3TC to CAB LA+RPV LA. • Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study (refer to Time & Events Table). Results from these assessments may aid early detection of HSR. • Oral CAB will be withdrawn immediately for cases with suspected HSR during the oral lead-in phase. During oral and CAB LA treatment, any HSR reactions that occur would be managed supportively

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Development of Resistance following discontinuation of CAB LA	Residual concentrations of CAB would remain in the systemic circulation of participants for prolonged periods (more than 1 year in some participants, GlaxoSmithKline Document Number 2016N269422_00, Study 201120) 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.	• Alternative oral HAART regimens will be prescribed within four weeks after participants stop CAB LA. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimizing of the risk of emergent resistance. • The participants in this study who discontinue CAB LA for any reason will be monitored for a minimum of 52 weeks from the time of the last CAB LA 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	• 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
	- the antimycobacterials rifampicin, rifampin, 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. Residual concentrations of CAB could remain in the systemic circulation of participants who stopped treatment (e.g. for tolerability issues or treatment failure) for prolonged periods (months). Participants discontinuing a LA regimen may be at risk for developing DDIs many weeks after discontinuing injectable therapy.	

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 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 are currently unknown. 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), a PK sample, post dose ECG, 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 timepoints (Week 4b; Week 48; Week 96; Week 104b [participants transitioning from ABC/DTG/3TC]) 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 prescribing information [Edurant Prescribing Information, 2018].

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, the majority of ISRs have not, to date, been associated with an excess of participants' withdrawal due to ISRs.	• 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored. • Specialist dermatology consultation will be sought if warranted for individual participants.
Rash	Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are Grade 1 or Grade 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.	• At the beginning of this study, RPV LA administration was preceded by a four week oral RPV lead-in to evaluate safety and tolerability in individual participants. During the Extension Phase of the study, following review of available oral lead-in and Maintenance Phase safety data, the protocol was amended to allow an optional oral lead-in for the participants transitioning from ABC/DTG/3TC to CAB LA+RPV LA. • 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. • Participants experiencing a grade 3 or

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		4 rash should discontinue their ART medication and will be withdrawn from the study. • All rash events should be assessed 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.
Development of Resistance	Residual concentrations of RPV can remain in the systemic circulation of participants who stopped treatment (e.g. for tolerability issues or treatment failure) for more than one year in some participants [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 four weeks after participants stop RPV LA. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimizing of 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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 and 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 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. Residual concentrations of RPV could remain in the systemic circulation of participants who stopped treatment (e.g. for tolerability issues or treatment failure) for prolonged periods (months).	• 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
	Participants discontinuing a LA regimen may be at risk for developing resistance to RPV many weeks after discontinuing injectable therapy.	
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. The clinical consequences of overdose with RPV LA are currently unknown. 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), a PK sample, 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 timepoints (Week 4b; Week 48; Week 96; Week 104b [participants transitioning from ABC/DTG/3TC]) for determination of RPV concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of RPV concentrations.
Study Procedures		
Risks of complications from venipuncture for blood sampling	Complications from with venipuncture include swelling, bleeding, bruising and infection	• These risks will be minimized using current standard of care techniques for venipuncture.
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.	• ECGs will be conducted by appropriately trained personnel and effort made to minimise contact time for application of the pads.
Other		
Risk of Treatment Failure	This study employs a novel maintenance approach to the treatment of HIV-1 infection. Following virologic suppression, participants will be transitioned off of a 3 drug ART regimen to a 2 drug LA ART regimen that remains experimental. CAB and RPV have demonstrated antiviral activity in the Phase 2b studies LAI116482 (oral two drug treatment) and 200056 (two drug LA treatment). 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	• HIV-1 RNA 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	formulations and LA data from 200056. 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.	virologic response. • HIV-1 RNA will be closely monitored throughout the study.

4.6.2. 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 Brochure (please refer to Section 6 of the IB: 'Summary of Data and Guidance for the Investigator.')

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.

4.6.3. Benefit Assessment

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

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 Q4W dosing without the need to take concomitant daily oral therapy. Adherence in these participants is expected to be improved and will be directly observed. 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 LA agents, has been demonstrated through Week 32 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.

4.6.4. 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 the CAB + RPV are justified by the anticipated benefits that may be afforded to study participants switching to a Long-Acting, NRTI-sparing regimen.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational product or other study treatment that may impact participant eligibility is provided in the current Investigator Brochures for CAB (GlaxoSmithKline Document Number RH2009/00003/07) and RPV (RPV IB, 2017), and the RPV product label (Edurant Prescribing Information, 2018). Information for ABC/DTG/3TC or DTG is provided in the current DTG IB (GlaxoSmithKline Document Number: RM2007/00683/11) and US or country product label (TRIUMEQ Prescribing Information, 2018; TIVICAY Prescribing Information, 2017).

5.1. Inclusion Criteria

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

In general, participants screened for this study must:

- be able to understand and comply with protocol requirements, instructions, and restrictions,
- be likely to complete the study as planned,
- understand the long term commitment to the study,
- and be considered appropriate candidates for participation in an investigative clinical trial with oral and intramuscularly injectable medications (e.g., no active substance abuse, acute major organ disease).

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility. 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. Similarly, if a central laboratory result cannot be generated for genotype/phenotype, a local result can be considered following review and approval by the study virologist.

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

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 initiation of antiretroviral therapy in accordance with local treatment guidelines.**

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

AGE
HIV-1 infected, ART-naive men or women aged 18 years or greater at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥1000 c/mL; Antiretroviral-naïve (≤ 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection). Any previous exposure to an HIV integrase inhibitor or non-nucleoside reverse transcriptase inhibitor will be exclusionary.
SEX
Female Participants: A female participant is eligible to participate if she is not pregnant at Screening and first day of Induction Phase (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test), 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 Appendix 7.) 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. **ALL participants** in the study should be counseled 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.

INFORMED CONSENT
Capable of giving signed informed consent as described in Section 6.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
OTHER
French participants: In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise 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 Medical Conditions
a. Women who are pregnant, breastfeeding, or plan to become pregnant or breastfeed during the study.
b. Any evidence at Screening of an active Centers for Disease and Prevention Control (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell count <200 cells/mm^3 are not exclusionary (local guidelines dictate).
Participants with known moderate to severe hepatic impairment.
Any pre-existing physical or mental condition (including substance abuse 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.
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.
Participant who, in the investigator's judgment, poses a significant suicide risk. Participant's recent history of suicidal behavior and/or suicidal ideation should be considered when evaluating for suicide risk.
The participant has a tattoo or other dermatological condition overlying the gluteus

region which may interfere with interpretation of injection site reactions.

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.

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 prior to Week 48 of the Maintenance Phase 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, HCV 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 is inconclusive, the Fib-4 score will be used to verify eligibility.
    - A 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 (√ALT))

Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

History of liver cirrhosis with or without hepatitis viral co-infection.

Ongoing or clinically relevant pancreatitis.

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.

Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the study Medical Monitor for inclusion of the participant prior to enrolment.

Any condition which, in the opinion of the Investigator, may interfere with the absorption, distribution, metabolism or excretion of the drug or render the participant unable to receive study medication.

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.

Current or anticipated need for chronic anti-coagulation.

Alanine aminotransferase (ALT) ≥3 times ULN.

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.

CONCOMITANT MEDICATIONS

Exposure to an experimental drug and/or experimental vaccine within 28 days or 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP.

Treatment with any of the following agents within 28 days of Screening:

- radiation therapy
- cytotoxic chemotherapeutic agents
- tuberculosis (TB) therapy, with the exception of treatment of latent TB with isoniazid
- Immunomodulators that alter immune responses (such as chronic systemic corticosteroids, interleukins, or interferons). Note: Participants using short-term (e.g. ≤21 day) systemic corticosteroid treatment; topical, inhaled or intranasal corticosteroids are eligible for enrolment.

Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening.

Treatment with any agent, except recognized ART as allowed above, with documented activity against HIV-1 within 28 days of the first dose of IP.

Use of medications which are associated with Torsades de Pointes (See SPM for a list of relevant medications).

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
Any evidence of primary resistance to NNRTIs (except for K103N which is allowed), or any known resistance to INIs from historical resistance test results (International AIDS Society [IAS]-USA, 2015). Note: re-tests of Screening genotypes are allowed only at the discretion of the study virologist.
Participants who are *HLA-B*5701* positive and are unable to use an NRTI backbone that does not contain abacavir (participants who are *HLA-B*5701* positive may be enrolled if they use a NRTI backbone that does not contain abacavir; *HLA-B*5701* positive participants may be excluded from the study if local provision of an alternate NRTI backbone is not possible).
Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening Phase to verify a result.
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.
Participant has estimated creatinine clearance <50 mL/min/1.73m^2 via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, 2009).
Participants who are currently participating in or anticipate to be selected for any other interventional study.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently enrolled or 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 7.4.3.6).

5.4. Withdrawal/Stopping Criteria

Participants permanently discontinuing study treatments prior to Week 100 are considered to be withdrawn from the study treatments. Similarly, participants permanently discontinuing participation from the Extension Phase prior to commercially available CAB LA + RPV LA drug supply are considered to be withdrawn from the study treatments, and will move directly into the Long-Term Follow-Up Phase. Participants permanently discontinuing participation from the Long-Term Follow-Up Phase are considered to be withdrawn from the study treatments and from the study.

A participant may withdraw consent and discontinue participation in this study at any time. The Investigator may also, at their discretion, discontinue the participant from participating in this study at any time (e.g., safety, behavioral 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. Participants who are withdrawn from the study 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.

Reasons for study withdrawal <u>may</u> include:

- Adverse event / Serious adverse event
- Protocol deviation
- Intolerability of injections
- Participant lost to follow-up
- Participant withdrew consent
- Investigator discretion
- 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 <u>must</u> be withdrawn 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.
- Participants who cannot or do not wish to continue on to the Long-Term Follow Up Phase.
- Confirmed virologic failure.
- Pregnancy (intrauterine), regardless of termination status of the pregnancy. (If receiving CAB LA + RPV LA, the participant would discontinue LA study treatment and continue to be followed in the Long-Term Follow-Up Phase.) *As a reminder, females of reproductive potential who changed their minds and desire to be pregnant, or who state they are no longer willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.*

- Participant requires a second switch or a dose adjustment of any component of the ABC/DTG/3TC (with exception of dose reduction for renal insufficiency as noted in Section 4.2.7). A substitution for NRTI backbone is allowed at Screening, e.g. ABC/3TC to TDF/FTC or TAF/FTC for participants who are *HLA-B*5701* positive. During the Induction Phase, prior to randomization into the Maintenance Phase at Day 1, one switch to an alternate approved background NRTI therapy is allowed for toxicity or tolerability management.
- 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).
- Grade 4 clinical AE or toxicity in the absence of compelling evidence that the AE is not causally related to the IP.
- Liver toxicity where Stopping Criteria are met and no compelling alternative cause is identified (See Section 5.4.1).
- Renal toxicity is met and no compelling alternate cause is identified.
- Participant has a Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement.
- The following QT criteria:
    - Corrected QT interval (QTc) >550 msec considered causally related to IP (See Section 5.4.2).

This criterion must be based on the average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief Phase, and then use the averaged QTc values of the three ECGs to determine whether the participant should be discontinued from the study.

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 (Table 5) 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".

5.4.1. 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.

5.4.1.1. 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 critera is met, do the following:

- Immediately hold IP. If receiving 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, Table 7).
- 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 eCRF 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.

5.4.1.2. Liver Event Adjudication Committee

A liver safety panel will be used to evaluate all subjects 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 analyses, estimated timing and the decision criteria will be pre-specified in an Adjudication Committee Charter.

5.4.1.3. 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.

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.

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 of drug or continuation of LA dosing 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.

5.4.2. 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.

5.4.3. Virologic Failure

Following randomization into the Maintenance Phase, no changes, or intensification of ART will be permitted prior to protocol-defined virologic failure (one switch allowed during Induction Phase for toxicity / tolerability management – See Section 6.8). 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 the first day of the Induction Phase. 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 potential emergence of virologic resistance only.

5.4.4. Definition of Virologic Failure

For the purposes of clinical management in this study, virologic failure is defined as **any** of the following:

- Non-response as indicated by a less than a 1.0 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA after 4 weeks of starting the Induction Phase, which is subsequently confirmed, unless the plasma HIV-1 RNA is < 400 c/mL (Induction Phase criteria).
- Rebound as indicated by two consecutive plasma HIV-1 RNA that are > 0.5 $\log_{10}$ c/mL increase in plasma HIV-1 RNA from the nadir value on study, where the

lowest HIV-1 RNA value is ≥ 200 c/mL (Induction Phase criteria).

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

5.4.5. Managing Virologic Failure

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).

5.4.5.1. 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 key analysis timepoints (Week 48, Week 96) must return to the clinic as soon as possible (but no more than 4 weeks from 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 (e.g. if additional injections should be administered).

5.4.5.2. Suspected Virologic Failure

Upon notification that a participant's HIV-1 RNA plasma level meets any of the definitions of suspected 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 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.

5.4.5.3. Confirmed Virologic Failure

Participants who have confirmed virologic failure must be discontinued from the Induction, Maintenance or Extension Phase of 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 4.2.6).

A plasma sample from the suspected virologic failure visit as well as the first day of the Induction Phase (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.

5.5. 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.

Participants are considered to have completed the study if they satisfy one of the following:

- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including the Week 100 visit, and did not enter the Extension Phase;
- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including the Week 100 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).

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 Long-Term 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 ABC/DTG/3TC with ongoing AEs, 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.

In this study, investigational product (IP) refers to oral ABC/DTG/3TC single tablet regimen (or alternately DTG), oral CAB, and CAB LA, which will be supplied by GlaxoSmithKline and oral RPV and RPV LA which will be supplied by Janssen Pharmaceuticals. The dual NRTI background therapy that is administered with single entity DTG is not considered IP.

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 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. Cabotegravir (CAB) – Tablet

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 according to the product label.

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

6.1.2. Rilpivirine (RPV) - Tablet

RPV [Edurant Prescribing Information, 2018) 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 globally marketed product, including US and the European Union. RPV will be overlabeled and packaged in bottles of 30 tablets. RPV tablets are to be stored according to the product label.

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.

6.1.3. Cabotegravir – Injectable Suspension (CAB LA)

CAB LA is manufactured by GlaxoSmithKline and is a sterile white to slightly pink suspension containing 200 mg/mL of CAB 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 according to the product label.

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

6.1.4. 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 aluminium 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 stored according to the product label and should 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.

6.1.5. ABC/DTG/3TC STR - Tablet

ABC/DTG/3TC STR is manufactured by GlaxoSmithKline. Each film-coated tablet contains abacavir sulphate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg dolutegravir, and 300 mg of lamivudine. ABC/DTG/3TC tablets are purple, biconvex, oval, debossed with "572 Tri" on one side. ABC/DTG/3TC will be packaged in bottles of 30 tablets. ABC/DTG/3TC should be stored and dispensed in the original container, protected from moisture, are packaged with a desiccant which should not be removed. ABC/DTG/3TC tablets are to be stored according to the product label.

The inactive ABC/DTG/3TC tablet ingredients include D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet film-coating contains the inactive ingredients iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol – part hydrolyzed talc, and titanium oxide.

6.1.6. Dolutegravir (DTG) – Tablet

Dolutegravir is manufactured by GlaxoSmithKline and will be provided to participants who are *HLA-B*5701* positive (to be used in combination with 2 NRTIs). DTG 50 mg tablets are yellow, round, biconvex, film-coated tablets. The tablets contain 52.62 mg dolutegravir sodium salt, which is equivalent to 50 mg dolutegravir free acid. Each tablet is debossed with "SV 572" on one side and "50" on the other side. The tablets are packaged into high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each bottle contains 30 tablets and a desiccant. DTG tablets are to be stored according to the product label.

Each tablet of DTG also contains the following inactive ingredients: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

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.

At the beginning of the Maintenance Phase, 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 eligibility to continue into the Maintenance Phase, 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 LA + RPV LA or to remain on ABC/DTG/3TC through Week 100, in accordance with the computer generated randomization schedule. Randomization will be stratified by participants' Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) and gender at birth. In addition, RAMOS NG will facilitate the initial supply and subsequent resupply of IP to study sites.

6.3. Dose and Administration

At Day 1 (beginning of Maintenance Phase), participants will be randomly assigned to receive treatment with CAB LA + RPV LA or to remain on ABC/DTG/3TC. ABC/DTG/3TC dosing on Day 1 should 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 ABC/DTG/3TC prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned on Day 1. Regardless of treatment arm assignment, the investigator should instruct all participants on the importance of treatment adherence. This study has an open-label design. Following is a table of dosing and administration for all treatment arms:

Induction Phase (Week [-20] to Day 1) – All Subjects	
Week (-20) to Day 1 (1 tablet once daily)	Take 1 tablet ABC 600 mg / DTG 50 mg / 3TC 300 mg once daily *with or without food* **Take Day 1 dose after randomization.*
Maintenance Phase (Day 1 to Week 100)	
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 Injection (Loading Dose) – Week 4b^	
Week 4b^ (two 3 mL injections once)	Receive last dose of **oral** CAB + RPV 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 following Week 4b	
Week 8 to Week 100 (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
ABC/DTG/3TC Once Daily Arm*	
Day 1 to Week 100 (1 tablet once daily)	Take 1 tablet ABC 600 mg / DTG 50 mg / 3TC 300 mg once daily *with or without food* **Take Day 1 dose after randomization.*
Extension Phase (Week 100 through End of Study)	
CAB LA + RPV LA Arm – continue IM dosing Every 4 Weeks+	
ABC/DTG/3TC Arm (Transition to CAB LA + RPV LA)* - Optional Oral Lead-In	
Dosing If Using Optional Oral Lead-In	
Week 100 to Week 104b (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 Injection (Loading Dose) – Week104b^ - Optional Oral Lead-In	
Week 104b^ (two 3 mL injections once)	Receive last dose of oral CAB + RPV 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 following Week 104b – Optional Oral Lead-In	
Week 108 forward (two 2 mL injections every 4	Receive CAB LA 400 mg given as 1 X 2 mL IM injection

weeks)	Receive RPV LA 600 mg given as 1 X 2 mL IM injection
ABC/DTG/3TC Arm (Transition to CAB LA + RPV LA)*	
Direct to Inject Dosing - if *Not Using* Oral Lead-In	
First Injection (Loading Dose) – Week100^ - No Oral Lead-In	
Week 100^ (two 3 mL injections once)	Receive last dose of oral ABC/DTG/3TC 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 following Week 100 – No Oral Lead-In	
Week 104a 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 ABC/DTG/3TC will be given an option to switch to CAB LA + RPV LA (or be discontinued from the study) at Week 100. If the participant decides not to continue participation in the study, arrangements for off-study ART should be made in advance of this Week 100 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 study summary data, according to actual randomized treatment groups, will be available to sponsor staff prior to the planned Week 48 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 participants receiving oral treatment (ABC/DTG/3TC [or alternate DTG], oral CAB, oral RPV). Pill counts will not be done for the dual NRTIs taken with DTG, as these will not be provided centrally. IP accountability will be conducted each time the participant receives a new/refill supply of IP, when the participant completes oral CAB and RPV (including oral bridging supply), and through the Withdrawal visit, study completion, or Week 104b of the Extension 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 SPM.

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. Sites should gently invert the vials 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, CAB and RPV injections should be given on different sides of the body (e.g. left or right gluteus medius), or spaced approximately 2 cm from one another, from the site of any previous injection or any injection site reaction. The time, side, and location of injections 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 type. 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 loading dose IM regimen (CAB LA 600 mg + RPV LA 900 mg) within 2 hours of taking the last oral CAB + RPV dose where possible. The same should apply to participants switching from the oral regimen to an IM regimen at Week 104b.

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

In the event of suspected intravenous administration, a PK sample will also be drawn approximately 2 hours post dose for evaluation of CAB and RPV plasma concentrations.

Appropriate, confirmation of successful IM administration will also be captured in the eCRF.

Additional dosing instructions and considerations can be found in the SPM.

6.7. Compliance with Study Treatment Administration

IP accountability will be evaluated using pill counts of unused IP (CAB and RPV tablets at the end of oral dosing [including bridging supply], and ABC/DTG/3TC [or alternate DTG]). This assessment will be conducted each time the participant receives a supply of oral study medication. These data will be recorded in the participant's eCRF. Treatment start and stop dates will also be recorded in the eCRF.

When participants are dosed with CAB LA and RPV LA at the site, they will receive IM injections directly from the investigator or designee, under medical supervision. The date and time of each injection of CAB LA and RPV LA administered in the clinic will be recorded in the source documents. These data 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.

IP accountability (e.g. pill counts) will not be assessed for alternate NRTIs taken with single entity DTG, or during the Long-Term Follow-Up Phase.

Due to the long acting nature of the CAB LA and RPV LA, it will be imperative that the participant is compliant with dosing visits. As part of the screening and participant selection process, Investigators must discuss with potential participants the long-term commitments for the study, and the importance of adhering to treatment regimens.

Investigators must have plans in place for adherence counselling for both treatment arms.

6.8. Protocol Permitted Substitutions

Participants who are *HLA-B*5701* positive at the Screening visit are allowed to enter the study on DTG and an approved dual-NRTI backbone that does not contain abacavir (e.g. TDF/FTC or TAF/FTC). This regimen may be supplied regionally by GSK or reimbursement will be provided as needed.

During the Induction Phase, prior to randomization into the Maintenance Phase at Day 1, one switch to an alternate approved background NRTI therapy is allowed for toxicity or tolerability management. The date of a decision to switch the NRTI background therapy for toxicity or tolerability management must be documented in the eCRF. Switches of a background NRTI for any other reason are not permitted in the study. Local prescribing information should be consulted for information regarding use of alternative background medications.

For consistency with prescribing information, dose reductions of lamivudine (or emtricitabine if used as alternate NRTI) are permitted throughout the study in the context of renal insufficiency, e.g. as needed for creatinine clearance <50 mL/min (See Section 4.2.7. for additional information).

No other dose reductions, modifications, or changes in the frequency of any components of any regimen will be allowed during the Maintenance and Extension Phases of the study.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements are essential and required for study conduct.

6.8.1. Oral Bridging

In exceptional circumstances, to address pre-planned missed CAB LA + RPV LA dosing visits, following consultation with the Medical Monitor, Investigators may provide daily oral CAB 30 mg and RPV 25 mg as a short-term “bridging” strategy for subjects who have begun CAB LA + RPV LA and who will miss a subsequent scheduled LA injection. 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 subject 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

IP 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 RPV LA are anticipated to be at high 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 in some participants 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 (e.g. in the Long-Term Follow-Up Phase) 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 injections [Week 4b]). The first injections of CAB LA (600 mg) and RPV LA (900 mg) are administered at Week 4b (can be performed as soon as lab results from Week 4a become available). The second and third IM injections (CAB LA 400 mg + 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 injections occur within the window of Week 7 to Week 8, but not later than Week 8, and the third injections occur within the window of Week 11 to Week 12, but no later than Week 12. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, with a (+ or -) 7 day dosing window, from the projected visit date, being allowed (<u>but not preferred</u>). In addition, following the Week 12 injections, time 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. For the duration of the study, the injection visit schedule should be maintained according to the first IM injections given at Week 4b.

At one-week post dose visits (Week 5, Week 41, and Week 101), 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.**

Transition from ABC/DTG/3TC to IM Dosing into the Extension Phase:

Participants who were randomized to ABC/DTG/3TC and are eligible to enter the Extension Phase will transition to IM dosing at or after Week 100. The transition from ABC/DTG/3TC to CAB LA + RPV LA can be completed with or without an oral lead-in prior to commencement of injectable treatment. The participant decision will be taken in consultation with the investigator and appropriately documented. In order to ensure no interruption in study treatment, the transition into Extension should be performed as follows:

Participants Transitioning Directly to Injections in the Extension Phase:

Central lab results and safety parameters from the Week 96 visit must be available and reviewed for participants who choose to transition direct to injection. If a clinical chemistry retest is required based on Week 96 labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 96). Participants will remain on oral ABC/DTG/3TC until the Week 100 injection visit, and until any required Week 96 retest results are available for review.

At Week 100, eligible participants will take the last dose of ABC/DTG/3TC (or DTG + 2 NRTIs), and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg) as initial loading doses. Clinical chemistries will also be assessed at Week 100. At Week 101, participants will return to the clinic for PK and safety assessments including clinical chemistries. The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104a and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104a, but not later than Week 104a, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 108 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 Receiving Optional Oral Lead-In in the Extension Phase:

At Week 100, eligible participants who after discussion with the investigator, choose to receive the optional oral lead-in will begin a 4 week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily. It is not necessary to dose ABC/DTG/3TC on the day the participant begins the oral lead-in with CAB + RPV. However, if the participant takes ABC/DTG/3TC prior to coming into the clinic, initiation of oral CAB and RPV should continue as planned.

At Week 104a, assessments including clinical chemistries will be performed. At Week 104b, participants will return to clinic, take the last dose of oral CAB + RPV, and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg) (within 2 hours of the final oral dose of CAB + RPV). The Week 104b visit can be performed as soon as lab results from Week 104a become available. The second and third IM injections (CAB LA 400 mg + RPV LA 600 mg) will be performed at Week 108 and Week 112. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 107 to Week 108, but not later than Week 108, and the third injections occur within the window of Week 111 to Week 112, but no later than Week 112. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks (monthly) thereafter, with a (+ or -) 7 day dosing window, from the projected visit date, being allowed (but not preferred). In addition, following the Week 112 injections, time 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. For the duration of the study, the injection visit schedule should be maintained according to the first IM injections given at Week 104b.

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 (for all oral dosing in the Induction, Maintenance, and Extension Phases of the study). 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 the Long Term Follow Up are expected to occur as projected according to the last injection. There is no calendar defined visit window in the Long Term Follow Up Phase.

6.10. Discontinuation of Study Treatment

Participants unable to manage drug toxicity or tolerate investigational product must have IP discontinued.

6.10.1. Discontinuation of ABC/DTG/3TC

In the event of a discontinuation of an ABC-containing product for any reason, re-initiation of this drug should be undertaken with caution. Health care providers should obtain a complete history of the events surrounding the discontinuation of the ABC-containing product. If there are symptoms consistent with a hypersensitivity reaction, ABC must not be reinitiated. If there is no evidence of a prior reaction, the participant may restart treatment with the ABC-containing product. The participant and health care provider must be aware of the possibility of a rapid-onset hypersensitivity reaction upon reinitiation of ABC, which may be life-threatening or fatal, and the participant must be able to, if necessary, receive prompt medical evaluation (see also Section 7.4.5.12).

6.10.2. Discontinuation of CAB LA or RPV LA

Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinues IP must initiate treatment with HAART and enter the Long-Term Follow-Up Phase for 52 weeks of follow up (see Section 4.2.6.).

6.11. Treatment of Study Treatment Overdose

For this study, any tablet intake exceeding a total daily dose of CAB 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 participants receiving ABC/DTG/3TC, any tablet intake exceeding the protocol defined daily number of tablets (one tablet daily) will be considered an overdose. For participants receiving DTG + NRTIs, any tablet count exceeding the marketed dose in local prescribing information 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 to 3 hours post dose for safety monitoring. An ECG will be performed approximately 2 hours post dose. The Medical Monitor will be notified in the event of a suspected maladministration.

In the event of suspected intravenous administration, a PK sample will also be drawn approximately 2 hours post dose for evaluation of CAB and RPV plasma 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 GSK is unable to recommend specific treatment.

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

a. contact the Medical Monitor immediately.

closely monitor the participant for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until IP can no longer be detected systemically (number of days will vary by compound – Medical Monitor / study team can advise).

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).

document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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 (see Section 4.2.7 for information regarding dose modifications).

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.

6.13. Concomitant Medications and Non-Drug Therapies

Participants should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential drug:drug interactions between such treatments and the study drugs. The investigator should evaluate any potential drug:drug interactions at every visit, including reviewing the most current version of the investigator brochures, the U.S and/or local prescribing information for RPV, and ABC/DTG/3TC (or DTG + NRTIs), especially if any new concomitant medications are reported by participants. All concomitant medications, 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.

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 6.13.1). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician.

Because non-HIV vaccines may cause a temporary increase in the level of plasma HIV-1 RNA, it is highly 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 if possible (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.

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-Receptor antagonists (e.g. cimetidine, famotidine, nizatidine, ranitidine) may cause significant decreases in RPV plasma concentrations. 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.

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.

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

ABC/DTG/3TC: DTG should be administered 4 hours before or 6 hours after taking antacid or laxative products or sucralfate containing polyvalent cations (e.g., aluminum and magnesium) or calcium supplements. Proton pump inhibitors and H2-Receptor antagonists (e.g. cimetidine, famotidine, nizatidine, ranitidine) may be used in place of antacids with no dosing restrictions. Iron supplements can be taken with DTG provided that all three are taken together with a meal. Under fasting conditions, DTG should be given 2 hours prior to OR 6 hours after iron supplements.

Metformin concentrations may be increased by DTG. For participants starting metformin after DTG, titrate as recommended in local prescribing information for DTG and monitor glucose control. If starting DTG after metformin, consider dose reduction of metformin as needed if glucose is well controlled.

Clinical monitoring is recommended for participants taking methadone as methadone maintenance therapy may need to be adjusted in some participants.

Approved hormonal contraception may be administered. However, the investigator should consult local prescribing information for guidance on the use of hormonal contraceptives with background ART as some antiretrovirals have clinically significant drug interactions with these products.

Please refer to the local prescribing information for other drugs that should be used with caution, require dose adjustment, or increased clinical monitoring if taken with ABC/DTG/3TC.

DTG + 2 NRTIs: *For participants who are HLA-B*5701 positive and are receiving DTG +alternate NRTI background therapy or who have switched to alternate NRTI background therapy during the Induction Phase for tolerability, refer to local prescribing information for details regarding concurrent therapies.*

6.13.1. 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 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 participants with acute viral hepatitis (James, 2009).
- Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided due to the 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, but more than a single dose in a treatment course may cause a significant decrease in RPV plasma concentration and is prohibited. Topical, inhaled or intranasal use of glucocorticoids will be allowed.

- Hepatitis C infection therapy is prohibited during the Induction and Maintenance Phase before the Week 48 primary endpoint, and interferon-based HCV therapy is prohibited throughout the entire study. Options for treatment of hepatitis C should be discussed with the Medical Monitor prior to initiation of therapy.

Note: Any prohibited medications 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.

For additional information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy used during the study (e.g. ABC/DTG/3TC), please consult the current DTG Investigator brochure and local prescribing information.

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 RPV:

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

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.

Please refer to the current RPV Investigator brochure and local prescribing information for other drugs that are prohibited, should be used with caution, require dose adjustment, or increased clinical monitoring if taken with oral RPV.

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 aspirin (daily doses ≤325mg). Systemic anticoagulation (including prophylaxis doses) on the day of an IM injection should be avoided.

Concurrent with ABC/DTG/3TC

The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, the following medications must not be administered concurrently with DTG:

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

Dofetilide and pilsicainide are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide/pilsicainide concentrations and potential for toxicity.

Note: Any prohibited medication that decrease DTG 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. Any other prohibited medication should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

Please refer to the current DTG IB and local prescribing information for other drugs that should be used with caution, require dose adjustment, or increased clinical monitoring if taken with ABC/DTG/3TC (or DTG with alternate NRTI background therapy).

Concurrent with DTG + NRTIs

In addition to the prohibited medications noted for DTG above (as a component of ABC/DTG/3TC), for participants who are *HLA-B*5701* positive and who are receiving DTG + alternate NRTI background therapy, refer to the current DTG IB and 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 may be altered during the course of the study based on newly available data to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- 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 primary endpoint (Week 48), 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 at Week 112, the schedule of assessments for participants continuing in the Extension Phase from the CAB LA + RPV LA arm will be modified to collect clinical chemistries, HIV-1 RNA, and CD4+ cell count every 12 weeks.

Participants originally randomized to ABC/DTG/3TC at Day 1, who choose to continue into the Extension Phase and transition to CAB LA + RPV LA, will have all assessments noted in the Time and Events table below performed Q4W through Week 124. Beginning at Week 124, the schedule of assessments for these participants transitioning from ABC/DTG/3TC into the Extension Phase will be modified to collect clinical chemistries, HIV-1 RNA, and CD4+ cell count every 12 weeks as noted in the Time and Events schedule below.

From Week 124 forward, all participants (from both originally randomized treatment arms), will have the same schedule of events (same visits, same assessments, same time frame).

Table 5 201584 (FLAIR) Time and Events Table

Procedures	Screening a	Induction Phase by Week					Maintenance Phase by Week																Extension Phase by Week								Withdrawal[y]	Long-Term Follow-Up
		Baseline (-20)	(-16)	(-12, -8)	(-4)	WDy	Day 1	4a	4b – LA arm	5t – LA arm	8, 12, 16, 20	24	28, 32, 36	40, 44	41 – LA arm	48	52 - LA Arm	56	60 – LA Arm	64, 72, 80, 88	68,76, 84, 92 - LA Arm	96	100	101 – Direct to Inject Arm	104a – Direct to Iniect Arm	104a LA and Oral Lead-In Arm	104b - Oral Lead-In Arm	108	112, 116, 120,124 ABC/DTG/3TC Switch Arm	Q4W after 108 (LA Arm) or after 124 (Switch Arm)	Q12W beginning 112 (LA Arm) or 124 (Switch Arm)[j]		
Clinical and Other Assessments																																
Written Informed Consent	X																															
Eligibility Verification (Inclusion / Exclusion Criteria)	X	X			X[b]																	X[b]										
Randomization							X																									
Demography	X																															
Medical History[c]	X																															
Medication History / Prior ART History	X																															
Symptom Directed Physical Exam and Medical	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedures	Screening a	Induction Phase by Week					Maintenance Phase by Week																Extension Phase by Week								Withdrawal[Y]	Long-Term Follow-Up
		Baseline (-20)	(-16)	(-12, -8)	(-4)	WDy	Day 1	4a	4b – LA arm	5t – LA arm	8, 12, 16, 20	24	28, 32, 36	40, 44	41 – LA arm	48	52 - LA Arm	56	60 – LA Arm	64, 72, 80, 88	68,76, 84, 92 - LA Arm	96	100	101 – Direct to Inject Arm	104a – Direct to Iniect Arm	104a LA and Oral Lead-In Arm	104b - Oral Lead-In Arm	108	112, 116, 120,124 ABC/DTG/3TC Switch Arm	Q4W after 108 (LA Arm) or after 124 (Switch Arm)	Q12W beginning 112 (LA Arm) or 124 (Switch Arm)[J]		
Assessment [d]																																
Weight, BMI, and Height [e]		X				X										X						X					X				X	
Cardiovascular Risk Assessment	X	X																														
Vital Signs (BP, HR, temperature) [f]	X	X				X	X									X						X					X				X	
12-Lead ECG [g]	X	X pre-dose x3				X	X		X							X [g]						X					X				X	
CDC Classification	X	X																														

Procedures	Screening a	Induction Phase by Week					Maintenance Phase by Week																Extension Phase by Week								Withdrawal[Y]	Long-Term Follow-Up
		Baseline (-20)	(-16)	(-12, -8)	(-4)	WDy	Day 1	4a	4b – LA arm	5t – LA arm	8, 12, 16, 20	24	28, 32, 36	40, 44	41 – LA arm	48	52 - LA Arm	56	60 – LA Arm	64, 72, 80, 88	68,76, 84, 92 - LA Arm	96	100	101 – Direct to Inject Arm	104a – Direct to Inject Arm	104a LA and Oral Lead-In Arm	104b - Oral Lead-In Arm	108	112, 116, 120,124 ABC/DTG/3TC Switch Arm	Q4W after 108 (LA Arm) or after 124 (Switch Arm)	Q12W beginning 112 (LA Arm) or 124 (Switch Arm)[j]		
HIV Associated Conditions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE and SAE Assessment, Con Meds	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISR Assessment (LA Arm Only)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X If appli-cable
Columbia Suicide Severity Rating Scale (eC-SSRS)[i]	X	X			X	X	X		X		X	X	X	X		X			X	W72	W84	X										X	
Clinical Chemistry and Hematology	X	X	X	X	X	X	X	X			X	X	X	X		X	X	X	X	X		X	X		X	X		X	X		X	X	X
Rapid Plasma Reagin (RPR)	X	X																															

Procedures	Screening a	Induction Phase by Week					Maintenance Phase by Week																Extension Phase by Week								Withdrawal[y]	Long-Term Follow-Up
		Baseline (-20)	(-16)	(-12, -8)	(-4)	WDy	Day 1	4a	4b – LA arm	5t – LA arm	8, 12, 16, 20	24	28, 32, 36	40, 44	41 – LA arm	48	52 - LA Arm	56	60 – LA Arm	64, 72, 80, 88	68,76, 84, 92 - LA Arm	96	100	101 – Direct to Inject Arm	104a – Direct to Iniect Arm	104a LA and Oral Lead-In Arm	104b - Oral Lead-In Arm	108	112, 116, 120,124 ABC/DTG/3TC Switch Arm	Q4W after 108 (LA Arm) or after 124 (Switch Arm)	Q12W beginning 112 (LA Arm) or 124 (Switch Arm)[j]		
Pregnancy Testing[j]	S	U	S	S	S	S	U	S	U		S	S	S	S		S	S	S	S	S	S	S	S U[j]		S	S	U	S	S	S - Q4 W		S	S
HIV-1 RNA and sample for storage[k]	X[k]	X	X	X	X	X	X		X		X	X	X	X		X	S[k]	X	X	X		X	S[k]		X		X	X	X		X	X	X	X
CD4+	X	X	X	X	X	X	X		X		X	X	X	X		X		X	X	X		X					X	X	X		X	X	X	X
CD8+		X			X		X		X			X				X						X					X						X	
Urinalysis[l]		X					X	X				X				X						X				X							X	
Fasting Lab Assessments: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [m]		X					X									X						X					X						X	

Procedures	Screening a	Induction Phase by Week					Maintenance Phase by Week															Extension Phase by Week								Withdrawal[y]	Long-Term Follow-Up
		Baseline (-20)	(-16)	(-12 -8)	(-4)	WDy	Day 1	4a	4b – LA arm	5t – LA arm	8, 12, 16, 20	24	28, 32, 36	40, 44	41 – LA arm	48	52 - LA Arm	56	60 – LA Arm	64, 72, 80, 88	68,76, 84, 92 - LA Arm	96	100	101 – Direct to Iniect Arm	104a – Direct to Iniect Arm	104a LA and Oral Lead-In Arm	104b - Oral Lead-In Arm	108	112, 116, 120,124 ABC/DTG/3TC Switch Arm	Q4W after 108 (LA Arm) or after 124 (Switch Arm)	Q12W beginning 112 (LA Arm) or 124 (Switch Arm)[j]		
Hepatitis B (HBsAg), Anti-HBc, and Anti-HBsAG Hepatitis C (anti-HCV Ab)	X																															
*HLA-B*5701*	X																															
PT/PTT/INR	X	X																														
Renal and Bone marker analytes (blood/urine)[n]							X									X						X									X	
Peripheral Blood Mononuclear Cells (PBMCs)[o]							X															X									X	
Genetic Sample[p]		X																														

Procedures	Screening a	Induction Phase by Week					Maintenance Phase by Week																Extension Phase by Week								Withdrawal[y]	Long-Term Follow-Up
		Baseline (-20)	(-16)	(-12, -8)	(-4)	WDy	Day 1	4a	4b – LA arm	5t – LA arm	8, 12, 16, 20	24	28, 32, 36	40, 44	41 – LA arm	48	52 - LA Arm	56	60 – LA Arm	64, 72, 80, 88	68,76, 84, 92 - LA Arm	96	100	101 – Direct to Inject Arm	104a – Direct to Inject Arm	104a LA and Oral Lead-In Arm	104b - Oral Lead-In Arm	108	112, 116, 120,124 ABC/DTG/3TC Switch Arm Q4W after 108 (LA Arm) or after 124 (Switch Arm)	Q12W beginning 112 (LA Arm) or 124 (Switch Arm)[j]			
Pharmacokinetics (CAB + RPV only)																																
PK Sample (S)= Storage sample									X [v w]	X [t v]	X	X	X	X	X [v]	X [v]	X	X	X	S		X [v]	X	X [v]	X		X [v w]	S				X	S
Investigational Products																																
Oral CAB and Oral RPV Dispensation							X	X															X[x] OLI Only			X[x] OLI Only							
ABC/DTG/3TC Dispensation (or DTG alternate)		X	X	X	X [q r]		X	X			X	X	X	X		X		X		X		X										
Study Treatment Accountability (pill counts)			X	X	X [r]	X	X	X	X [u]		X	X	X	X		X		X		X		X	X OLI Only			X OLI Only	X [u]					
IM Study Treatment Administration –									X		X	X	X	X		X	X	X	X	X	X	X	X		X	X	X [s]	X	X	X – cont			

Procedures	Screening a	Induction Phase by Week					Maintenance Phase by Week															Extension Phase by Week								Withdrawal[Y]	Long-Term Follow-Up
		Baseline (-20)	(-16)	(-12, -8)	(-4)	WDy	Day 1	4a	4b – LA arm	5t – LA arm	8, 12, 16, 20	24	28, 32, 36	40, 44	41 – LA arm	48	52 - LA Arm	56	60 – LA Arm	64, 72, 80, 88	68,76, 84, 92 - LA Arm	96	100	101 – Direct to Inject Arm	104a – Direct to Iniect Arm	104a LA and Oral Lead-In Arm	104b - Oral Lead-In Arm	108	112, 116, 120,124 ABC/DTG/3TC Switch Arm	Q4W after 108 (LA Arm) or after 124 (Switch Arm)	Q12W beginning 112 (LA Arm) or 124 (Switch Arm)[j]		
Q4W throughout Maintenance and Extension Phase																														dos -ing Q4 W			
Patient Reported Outcomes[z]																																	
HAT-QoL (short form)							X					X				X						X									X	
SF-12							X					X				X						X									X	
ACCEPT							X				W 8	X				X						X									X	
HIVTSQ(s)							X		X			X		W 4 4								X									X	
HIVTSQ(c)																X															X	
PIN (LA Arm Only)[aa]										X					X	X						X									X	
NRS (LA Arm									X	X				W	X							X										

Procedures	Screening a	Induction Phase by Week					Maintenance Phase by Week																Extension Phase by Week								Withdrawal[Y]	Long-Term Follow-Up
		Baseline (-20)	(-16)	(-12, -8)	(-4)	WDy	Day 1	4a	4b – LA arm	5t – LA arm	8, 12, 16, 20	24	28, 32, 36	40, 44	41 – LA arm	48	52 - LA Arm	56	60 – LA Arm	64, 72, 80, 88	68,76, 84, 92 - LA Arm	96	100	101 – Direct to Inject Arm	104a – Direct to Inject Arm	104a LA and Oral Lead-In Arm	104b - Oral Lead-In Arm	108	112, 116, 120,124 ABC/DTG/3TC Switch Arm	Q4W after 108 (LA Arm) or after 124 (Switch Arm)	Q12W beginning 112 (LA Arm) or 124 (Switch Arm)[j]		
Only)														40																			
Preference (LA Arm Only)																X																	

Follow Up Visit: Conduct ~4 weeks after the last dose of oral IP. Required only if the participant has ongoing AEs / lab abnormalities at the last on-study visit. This visit may be conducted by telephone.
Direct to Inject: Participants transitioning into the Extension Phase who do *not* use the optional CAB + RPV oral lead-in beginning at Week 100.
Oral Lead-In: Participants transitioning into the Extension Phase who do use the optional CAB + RPV oral lead-in beginning at Week 100.
LA Arm: Participants who were originally randomized to CAB LA + RPV LA at Day 1.
Switch Arm: All participants who transition into the Extension Phase from ABC/DTG/3TC (or DTG + 2 NRTI's) at Week 100 – e.g., both direct to inject and oral lead-in participants.

a. Complete all Screening assessments within 35 days. Participants may begin the Induction Phase as soon as all Screening assessments are complete. Participants may be rescreened once and will be assigned a new participant number.
b. Confirmation of eligibility to enter the Maintenance Phase (Section 4.2.4), eligibility to enter the Extension Phase (Section 4.2.5).
c. 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 and neurologic disorders.
d. 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 participant management and / or care.
e. Height collected at Baseline only.
f. Measure vital signs after about 5 minutes of rest in a semi-supine position.

g. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes. Perform ECG at Baseline (Week [-20]) in triplicate prior to dosing. For subjects randomized to CAB LA + RPV LA, at Week 4b and Week 48, a second ECG will be obtained approximately 2 hours after the last injection and just prior to the 2 hour post dose PK sampling.
h. Collect SAEs at Screen only if associated to study participation.
i. On Day 1, the eC-SSRS is to be administered prior to randomization. During the Maintenance Phase, the eC-SSRS will be administered at each Q4W visit through the Week 48 primary endpoint, and then followed by Q12W assessments for CAB LA + RPV LA arm, thereafter through Week 96 (LA: Week 60, 72, 84, 96). The ABC/DTG/3TC arm will have assessments at Week 72 and Week 96). Preferably completed at the beginning of the visit following administration of other patient reported questionnaires required prior to injections.
j. Conduct pregnancy tests for only women of childbearing potential at every visit throughout the study, including Q4W during the Extension Phase. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements. A negative urine pregnancy test is required prior to beginning the Induction Phase (Week [-20]), on Day 1 (preferably prior to randomization), and at Week 4b (or Week 104b for subjects transitioning from ABC/DTG/3TC) prior to the first injection. Serum pregnancy test can substitute for urine pregnancy test if locally required, but must be appropriately timed to confirm pregnancy status prior to e.g. randomization and first IM administration. S=Serum/U=Urine.
k. Plasma for storage will be used: to determine genotypic eligibility at Screen, for possible future analyses, as back- up in case samples are lost or damaged in transit to the lab and for genotypic and phenotypic analyses in cases of virologic failure. 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.
l. A morning specimen is preferred. To assess biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
m. Overnight fast is preferred; however, a minimum of a 6 hour fast is acceptable.
n. 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
o. Whole blood/Peripheral Blood Mononuclear Cell collection samples may be used for virologic analyses as described in Section 7.8. PBMCs will be collected at Day 1, Week 96, Withdrawal visits.
p. Informed consent for genetic research must be obtained before sample collection. Sample may be collected at any visit after signing informed consent, but preferably at the Week [-20] visit.
q. Instruct participants to continue to take the ABC/DTG/3TC regimen until Day 1 of the Maintenance Phase. Participants will be randomized at Day 1 to continue on ABC/DTG/3TC arm or begin oral CAB + oral RPV. Day 1 dosing should occur after randomization to determine defined treatment for the Maintenance Phase.
r. Remind participants of the potential change in study treatment and visit frequency beginning at Day 1.
s. Visit Week 104b is only required for participants transitioning from the ABC/DTG/3TC arm.
t. The Week 5 visit should be performed approximately 7 days after the first injections at Week 4b (3 to 10 day window allowed).
u. For oral CAB + RPV only.
v. Take PK samples pre-dose. At Week 4b (and Week 104b for participants transitioning to LA from ABC/DTG/3TC using the optional oral lead-in), the pre-dose PK sample should be taken after review of the PK diary and prior to the final oral CAB + RPV dose. A sample will be also be taken at Week 4b, Week 48, and Week 96 (and Week 100 [direct to inject] or Week 104b [using CAB + RPV oral lead-in]), approximately 2 hours post-injections. The Week 5, Week 41, and Week 101 visit can be performed at any time from 3 to 10 days after the Week 4b, Week 40, and Week 100 injection, respectively. PK samples at Week 5, Week 41, and Week 101 can be taken at any time during the visit.
w. Participants should take the last dose of oral CAB+RPV at Week 4b (and Week 104b for participants transitioning to LA from ABC/DTG/3TC if using the optional oral lead-in) in the clinic after PK sampling. Participants should take the last dose of ABC/DTG/3TC at Week 100 if transitioning directly to injections at Week 100. Injections should be administered within 2 hours of the last oral dose where possible.

x. For participants transitioning to CAB LA + RPV LA from ABC/DTG/3TC only.
y. Follow Up Visit: Conduct approximately 4 weeks after the last dose of oral 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.
z. With the exception of the NRS questionnaire, patient reported questionnaire/surveys are recommended to be administered at the beginning of the visit before any other clinical assessments are conducted, and prior to completion of the eCSSRs assessments. Only conduct questionnaires/surveys at Withdrawal if occurring prior to Week 96 (The NRS will not be collected at Withdrawal).
aa. The PIN, Preference, and NRS questionnaires are to be administered only to participants receiving CAB LA + RPV LA injections. The NRS should be collected 30 to 60 minutes post-injection (and at Week 5 and Week 41, one week post-injections) - the participant should record the maximum level of pain experienced with the most recent injections.

Note: BMI- Body mass Index, 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.

Participants must be counseled on the practice of safer sexual practices including the use of effective barrier methods (e.g. male condom/spermicide) and the length of time in which they are required for participation in this study as part of the eligibility process.

7.2.1. Screening

All participants will complete the Screening phase of up to 35 days prior to Baseline (Week [-20]) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. All Screening results **must** be available prior to enrolment. A single repeat of a procedure/lab parameter is allowed to determine eligibility (unless otherwise specified).

Eligibility criteria must be carefully assessed at the Screening visit and confirmed at the first Induction Phase visit prior to enrolment. Participants may enroll and begin the Induction Phase as soon as all Screening assessments are complete and the results are available and documented.

Laboratory results from the central laboratory services provided by this trial will be used to assess study eligibility. 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.

Each participant screened will be assigned a participant number. Participants not meeting all inclusion and exclusion criteria at initial screen may be re-screened one time with a new participant number. Participants who are enrolled into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

At Screening, samples for HIV-1 genotypic and phenotypic resistance testing and plasma HIV-1 RNA measurement will be obtained. If a central laboratory result cannot be generated for Screening genotype/phenotype, a local result can be considered following review and approval by the study virologist.

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

Participants infected with hepatitis B virus (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 prior to Week 48 of the Maintenance Phase of the study must not be enrolled into this study, as HCV therapy may include the prohibited medication interferon. The length of this study should be considered when assessing the potential need for therapy.

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. 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.

The electronic Columbia Suicidality Severity Rating Scale (eC-SSRS) (see Section 7.4.6) 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 is not necessarily exclusionary, rather a means to assess overall risk.

7.2.2. Baseline Assessments

Participants will have "Baseline" assessments completed at the beginning of the Induction Phase (Week [-20] visit).

Any changes to the eligibility parameters must be assessed and any results required must be available and reviewed prior to enrolment (e.g. urine pregnancy test for women of child bearing potential).

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

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

- cardiovascular risk factors (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);
- 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 (e.g. history of seizures).

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 in Adults (see Section 12.4).

7.4. Safety

7.4.1. Clinical evaluations

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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 first day of the Induction Phase 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 resting for about 5 minutes. At the first day of the Induction Phase, 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. 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. 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.
- Regular monitoring of hematology, blood chemistry, urinalysis and fasting glucose and lipids (parameters to be tested listed below).
- Periodic assessment of glucose, and bone and renal markers**.**
- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP at the beginning of the Induction Phase, prior to the first 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 Phase 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 7.4.6).

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 Table 5), 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 labelled 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 participant 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.

Following are the 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 (inorganic phosphorus)	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]
Follicle stimulating hormone (FSH) and estradiol (only in instances when postmenopausal status is questionable)
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate
Genetic 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]

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO_2 = 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. 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.
f. CD8+ cells will only be reported at Baseline (Week [-20]), Week (-4), Day 1, Week 4b, Week 24, Week 48, Week 96, and Withdrawal. Additionally, participants transitioning from the ABC/DTG/3TC arm to CAB LA + RPV LA will have CD8+ at Week 104b.
g. HBV DNA will only be performed for participants with a positive anti-HBc, 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 (Table 5).
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.

The definitions of an AE or SAE can be found in Section 12.6, Appendix 6.

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 ViiV/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 7.4.3.3), 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.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.6.
- 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.

NOTE: 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.

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 7.4.5) 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 5.4). Further information on follow-up procedures is given in 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 5.4.1. Additional information for reporting cardiovascular and death events is included in Section 7.4.3.7 and Section 7.4.3.8, respectively.

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	"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	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"
Seizure or suspected seizure	24 hours	eCRF	24 hours	eCRF
Suspected ABC HSR in participants randomized to the STR arm or receiving an oral ABC-containing regimen during the Long-Term Follow-Up Phase[a]	1 week	ABC HSR eCRF	1 week	Updated ABC HSR eCRF

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
ALT≥3×ULN **and** bilirubin≥2×ULN (>35% direct) (or ALT≥3×ULN)	24 hours[b]	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable[c]	24 hours	Updated "SAE" data collection tool/"Liver Event" documents[c]
ALT≥5×ULN that persists ≥2 weeks	24 hours[b]	Liver Event eCRF[c]	24 hours	Updated Liver Event eCRF[c]
ALT ≥8×ULN	24 hours[b]	Liver Event eCRF[c]	24 hours	Updated Liver Event eCRF[c]
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[b]	Liver Event eCRF[c]	24 hours	Updated Liver Event eCRF[c]

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.

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.
- 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.
- 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.

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.

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 (Section 12.4) 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, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 12.6.2), or
- The event or outcome 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 Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular (CV) events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported. The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms.

7.4.3.8. Death Events

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.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

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.

7.4.4. Toxicity Management

Adverse events that occur during the trial should be evaluated by the Investigator and graded according to the Division of AIDS (DAIDS) toxicity scales (See Section 12.2 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events"). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 7.4.3 and Section 12.6.

7.4.4.1. 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 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.

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 date of the first injection visit [Week 4b]). An additional (+ or -) 7 day window, from the projected visit date, is allowable from the third injections forward 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.

7.4.4.2. Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue IP at the discretion of the Investigator. (NOTE: See Section 7.4.5 "Specific Toxicities/Adverse Event Management" for exceptions to this guideline). Participants who choose to withdraw from 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 and RPV LA.

7.4.4.3. 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 7.4.5.1). Isolated Grade 3 lipid abnormalities do not require withdrawal of IP.

7.4.4.4. 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 7.4.5.1). 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.

7.4.5. Specific Toxicities / Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be associated with treatment of HIV infected participants are provided below.

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.

7.4.5.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event etiology during administration of IP and the follow-up period.

For a complete listing of stopping and follow-up criteria refer to Section 5.4.1. Additional guidance on restart/rechallenge can be found in Section 5.4.1.3 and Section 12.3, Appendix 3.

7.4.5.2. 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.

7.4.5.3. 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.

7.4.5.4. Seizures

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, and 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 page.

7.4.5.5. Creatine Phosphokinase (CPK) Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2 to 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 will initiate treatment with HAART enter the Long-Term Follow-Up Phase for 52 weeks of follow up.

7.4.5.6. 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.

7.4.5.7. 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 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 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.

7.4.5.7.1. Proximal Renal Tubule Dysfunction

Proximal Renal Tubule Dysfunction (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 Medical Monitor to discuss the rationale for restarting study drugs (if appropriate). 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.

7.4.5.8. 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 to 4 weeks. If confirmed, then consideration should be made for additional evaluation after consultation with the Medical Monitor. Additional evaluation may include a 24 hr 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 Medical Monitor should be immediately contacted. Further management should be agreed between the investigator and Medical Monitor.

7.4.5.9. 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.

7.4.5.10. 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 persist 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.

7.4.5.11. Allergic Reaction

Participants may continue IP 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 IP should permanently discontinue the IP 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 ABC/DTG/3TC 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.

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.

7.4.5.12. 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 TRIUMEQ. 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 participants, 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., TRIUMEQ, ZIAGEN, EPZICOM/KIVEXA or TRIZIVIR) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

7.4.5.12.1. Essential Participant 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. TRIUMEQ, ZIAGEN, EPZICOM / KIVEXA or TRIZIVIR) 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 TRIUMEQ, 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 TRIUMEQ, 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 TRIUMEQ, 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.

7.4.5.12.2. Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH), 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.

7.4.5.13. Rash Without ABC HSR Symptoms

Rash 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 participants taking ABC-containing products. These participants 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., TRIUMEQ, 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.

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 DTG IB [GlaxoSmithKline Document Number RM2007/00683/11] or local prescribing information.

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 ABC/DTG/3TC 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 Week 4b, 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.

7.4.6. 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 participants being treated with INIs, including ABC/DTG/3TC. 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 behavioral 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 participant 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 risk of and possible suicide related events.

7.4.7. Pregnancy

7.4.7.1. Pregnancy testing

Women of childbearing potential must have a negative pregnancy test at Screening, Baseline (Week [-20]), the first Induction Phase visit (Day 1), and Week 100 (if no oral lead-in is used) or Week 104b (if using CAB and RPV oral lead-in) for women transitioning into the Extension Phase from the ABC/DTG/3TC arm (prior to administration of first CAB LA and / or RPV LA injections). Pregnancy testing will also be conducted as per the Time and Events Table (Table 5) 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.

7.4.7.2. Time Period for Collecting Pregnancy Information

Pregnancy information will be collected after the start of the Induction Phase 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.

7.4.7.3. Action to be Taken if Pregnancy Occurs

Any female 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 4.2.6), after discussion with the Medical Monitor.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. 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 may 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. The 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.

7.4.8. Physical Exams

- 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.
- 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 7.4.5.10 for additional information.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.9. 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 heart rate. These will be recorded as per the Time and Events Table in Section 7.1.

7.4.10. Electrocardiogram (ECG)

- A 12-lead ECG will be performed in a semi-supine position. At the first day of the Induction Phase, 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 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. Refer to the Time and Events Table for collection timepoints (Table 5). Refer to Section 5.4.2 for [QTc] withdrawal criteria and additional [QTc] readings that may be necessary.

7.5. Pharmacokinetics

Plasma samples for determination of CAB and RPV concentrations will be collected throughout the Maintenance Phase and for the participants transitioning from the ABC/DTG/3TC arm in the Extension Phase of the study as noted in Table 8. Additional samples will be collected for storage during the Long-Term Follow Up Phase. 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 (2 mL each) and RPV (2 mL each) plasma concentrations will be collected from all participants randomized to receive CAB + RPV as described in Table 8.

At Week 4b (and Week 104b for participants using the oral CAB + RPV lead-in and transitioning into the Extension Phase from the ABC/DTG/3TC arm), PK samples must be collected within the window of 20 to 28 hours after the oral dose of CAB + RPV was taken the day prior to the clinic visit.

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 104b if transitioning into Extension Phase from ABC/DTG/3TC). The information from the diary card 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 final dose of oral CAB + RPV in the clinic at Week 4b (or Week 104b) after the pre-dose PK sample collection.

PK concentrations will be summarized, sources of variability examined, and used to explore 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[a]	Sample Times Relative to Dose
IM	CAB	Pre-Dose: Week 4b, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 96, 100, 108, Withdrawal 2 Hours Post Dose: Week 4b, Week 48, Week 96 1 Week Post Dose[b]: 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, 56, 60, 96, 100, 108, Withdrawal 2 Hours Post Dose: Week 4b, Week 48, Week 96 1 Week Post Dose[b]: Week 5 and Week 41 PK samples for storage only: Pre-dose: Week 64, 72, 80, and 88

Group	Analyte[a]	Sample Times Relative to Dose
		Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
ABC/DTG/3TC Arm Transitioning to CAB LA + RPV LA at Week 100 (participants using CAB + RPV oral lead-in)	CAB	Pre-Dose: Week 104b, Week 108 (for storage), Withdrawal 2 Hours Post Dose: Week 104b Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
	RPV	Pre-Dose: Week 104b, Week 108 (for storage), Withdrawal 2 Hours Post Dose: Week 104b Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
ABC/DTG/3TC Arm Transitioning to CAB LA + RPV LA at Week 100 (Direct to Inject - participants *not* using CAB + RPV oral lead-in)	CAB	Pre-Dose: Week 104a, Week 108 (for storage), Withdrawal 2 Hours Post Dose: Week 100 1 Week Post Dose[b]: Week 101 Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
	RPV	Pre-Dose: Week 104a, Week 108 (for storage), Withdrawal 2 Hours Post Dose: Week 100 1 Week Post Dose[b]: Week 101 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± 7 days (4th and all subsequent injections); Sample Collection: Pre-dose at Week 4b (and Week 104b for participants transitioning from ABC/DTG/3TC Arm using oral lead-in): 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.

a. Each analyte in individual collection tube.
b. Samples taken at Week 5, Week 41, and Week 101 may be collected from 3 to 10 days after Week 4b, Week 40, and Week 100, respectively. These samples may be collected at anytime during those visits.

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

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

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

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 Table 8 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 analysis for CAB concentration determination will be performed under the control of Platform Technology and Science (PTS), GlaxoSmithKline, the details of which will be included in the SPM. 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 SPM).

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 PTS, 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 analysed 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 biomarker assessments as outlined in the Time and Events Table (Table 5). Renal biomarkers include Cystatin C (blood), and 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. Since the intention is to utilize these biomarkers for research purposes, the Sponsor will not be reporting the results of these assessments to the investigator except for 25 hydroxy-vitamin D.

7.6.1. Biomarker Endpoints (Exploratory)

- Change from Baseline in renal and bone biomarkers at Week 48 and Week 96.

- Change from Baseline over time in eGFR using cystatin C and other renal biomarkers during the Maintenance Phase.

7.7. Genetics

Information regarding genetic research is included in Appendix 5.

7.8. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide "plasma for storage samples" and PBMCs according to the Time and Events Schedule in 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) and reverse transcriptase (RT), or with their GeneSeq Integrase and PhenoSense Integrase assays.

For Screening virologic evaluations, only viral genotype will be analyzed and this will be performed through the central laboratory.

7.8.1. HIV-1 pol Viral Genotyping and Phenotyping

At Screening, samples will be collected for HIV-1 RT and PRO genotype using a genotype assay and results will be provided to the Investigator to assist in the determination of participant eligibility.

Participants experiencing 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 both Baseline samples and from samples collected at the time of suspected virologic failure; these results will be reported to the Investigator as soon as available to provide guidance for election of a switch regimen.

7.8.2. HIV-1 Exploratory Analysis

Additional exploratory analyses for HIV-1 pol resistance may include viral genotyping and/or phenotyping on a representative subset of Baseline samples or virologic analysis on stored plasma samples from other time points. Analyses for HIV-1 resistance may, be carried out on peripheral blood mononuclear cell (PBMC) samples collected at Day 1 and Week 96 (or Withdrawal visit if prior to Week 96) and/or on stored plasma samples from other relevant time points. These analyses may also 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, super low HIV-1 RNA quantitation and measurement of viral replicative capacity. HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from all 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 (Table 5). 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).

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 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 participants in five European countries. The adaptation of the HIVTSQ included two additional items related to the mode of administration (ie: 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 HIVTSQ 12). 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 subjects) 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 participants 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 favorable perception of the injection, and 5 the most unfavorable.

The ACCEPT questionnaire is a generic medication acceptance measure assessing how participants weigh advantages and disadvantages of long-term medications (Marant, 2012). ACCEPT may be a predictor of participants' future adherence to and/or persistence with their treatment. While the ACCEPT questionnaire consists of 25 items that capture six dimensions, only the three questions that focus on general acceptance of study medication will be used in this study.

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, a shorter version adapted from the original version will be used. 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 to 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 "Preference" question will contain a single item exploring whether participants prefer the CAB LA + RPV LA injectable treatment or the current oral ART regimen.

Qualitative interviews may also be conducted regarding the subject's experience on the injection regimen. This would be conducted under a separate IRB/IEC 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 Week 4b, Week 24, Week 44, Week 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 Weeks 24, 48, 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 the tolerability of injections (using the NRS) at Weeks 5, 40, 41, 96.

7.9.2. Value Evidence and Outcomes Endpoints (Exploratory)

- The "Preference" question will be assessed at Week 48 (primary analysis) in participants randomized to the "CAB LA and RPV LA" arm to explore participant preference between CAB LA + RPV LA injectable regimen and ARV 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 MedDRA (Medical Dictionary for Regulatory Activities) 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

This study is designed to show that the antiviral effect of oral ABC/DTG/3TC followed by intramuscular CAB LA + RPV LA regimen is non-inferior to continuation of ABC/DTG/3TC at Week 48 of maintenance treatment. Non-inferiority in the proportion of participants with virologic failure at Week 48 (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/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 – ABC/DTG/3TC) is less than 6%.

If f_{la} is the failure rate on CAB LA + RPV LA and f_c is the failure rate on comparator arm 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 the continuation of ABC/DTG/3TC 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 c/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 ABC/DTG/3TC arm were 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, 201585, 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 (Center for Drug Evaluation and Research, Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment, 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 neighborhood of 4% are clinically tolerable, with typical observed rates of virological failure ranging from 1 to 3%.

As this study (201584) and study 201585 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 Snapshot response and failure rates observed in five recent stable switch studies are displayed in Table 9, all of which enrolled participants with at least 6 months of prior therapy. To inform the failure rates for early switch studies with INI-based regimens, for which no known relevant studies exist, the difference in snapshot failure rates between Week 48 and Week 96 observed in recent treatment naive studies with INI- based regimens are displayed in Table 10. These differences provide approximate predictions of the failure rates that may be observed for early switch studies enrolling participants with 48 weeks of prior initial therapy. Taken together, these data suggest that a reasonable assumption for the true failure rate for the ABC/DTG/3TC control arm is 2%, with no clear signal of differential failure rates between early and stable switch studies.

Table 9 Snapshot Analysis Outcomes in Recent Stable Switch Studies

Week 48			
Study	**Treatment Arm**	**HIV-1 RNA <50 c/mL**	**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. [Martinez, 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 2b 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 Phase) 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 overtime, 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 LA + RPV LA regimen compared to the control regimen.

Table 11 Snapshot Analysis Outcomes for Phase 2b CAB Studies (Intent-to-Treat Maintenance Exposed Population)

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

a. Participants had HIV-1 RNA <50 c/mL at Week (-4) and received oral CAB 30 mg + 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 30 mg + 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 have over 92% power to meet its primary objective.

Figure 8 Sensitivity of Estimated Power for Snapshot Virologic Failure

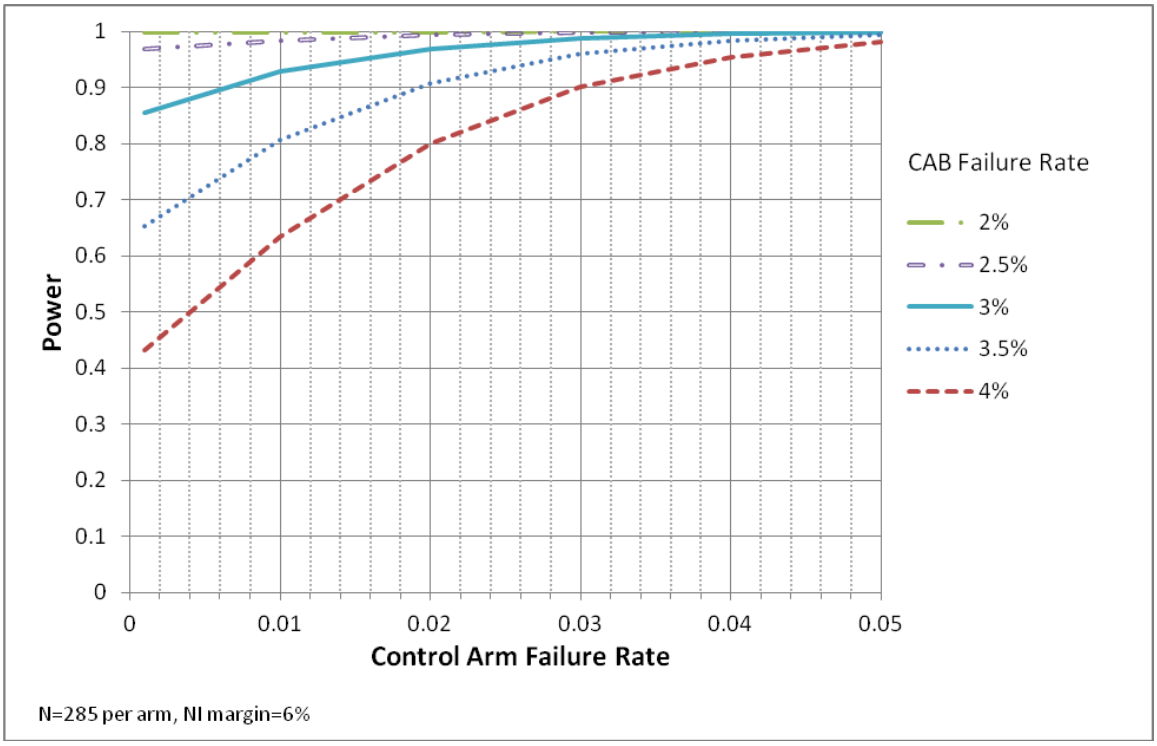


Table 12 shows power with 285 randomized per arm and the sample size required to guarantee 90% power, for a range of 'true' virologic failure rates. For instance, even if the failure rates were 3% for CAB LA + RPV LA and 1% for the control arm, the study will still have over 92% power to meet its primary 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 shows 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.

9.2.4. Sample Size Considerations for Week 124 Extension Switch Analysis

For the Week 124 Extension Switch population analysis (Section 9.3.1.6), the primary efficacy endpoint of interest is the proportion of participants without oral lead-in who have HIV-1 RNA ≥50 c/mL at Week 124 (i.e., 24 weeks from initiation of CAB LA + RPV LA, ±6-week analysis window, using the FDA Snapshot algorithm). The endpoint will be evaluated descriptively, with no formal statistical comparison to data generated in participants receiving oral lead-in by to initiation of CAB LA + RPV LA.

Table 14 presents the precision in estimation according to sample size and observed proportion with HIV-1 RNA ≥ 50 c/mL. For example, if the observed rate is 3% and 250 Extension switch participants do not receive oral lead-in, then the upper bound of the 95% CI would be 5.1%.

Table 14 Precision (Upper Limit of 95% CI) for Single Arm Proportion

Sample Size without Oral Lead-In	Observed Proportion HIV-1 RNA ≥ 50 c/mL	Upper limit of 95% Confidence Interval†
175	2%	4.1%
200	2%	3.9%
225	2%	3.8%
250	2%	3.7%
175	3%	5.5%
200	3%	5.4%
225	3%	5.2%
250	**3%**	**5.1%**
175	4%	6.9%
200	4%	6.7%
225	4%	6.6%
250	4%	6.4%

† Two-sided confidence Interval calculated using the Wald normal approximation method.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

9.3.1.1. All Participants Enrolled

The All Participants Enrolled population will consist of all enrolled participants who receive at least one dose of study drug in the Induction Phase. The All Participants Enrolled population will be the secondary population for some analyses.

9.3.1.2. Intent-to-Treat Exposed Population (ITT-E)

The ITT-E population consists of all randomized participants who receive at least one dose of IP during the Maintenance Phase of the study (on or after Day 1 visit).

Participants will be analyzed according to the randomized treatment regardless of what treatment was actually received. Unless stated otherwise, the population used in the primary efficacy analysis will be the ITT-E population.

9.3.1.3. Per-Protocol Exposed 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.

9.3.1.4. Safety Population

The Safety Population will consist of all randomized participants who receive at least one dose of IP during the Maintenance Phase of the study (on or after Day 1 visit). Participants will be assessed according to actual treatment received. Unless otherwise stated, the Safety Population will be used for safety analyses.

9.3.1.5. PK Population

The PK Population will include all participants who receive CAB and / or RPV and 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.

9.3.1.6. Extension Switch Population (ES)

The Extension Switch population will include all participants randomized to the Maintenance Phase ABC/DTC/3TC arm who switch to and receive at least one dose of CAB and/or RPV during the Extension Phase of the study. The ES population will be used to evaluate safety and efficacy of switching to CAB LA + RPV LA, with and without oral lead-in. Participants will be assessed according to actual treatment received during the Extension Phase.

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 LA + RPV LA – 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 comparisons 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 over time.

9.3.3. Planned Analyses

At least three analyses will be conducted to evaluate the objectives of the protocol: after all randomized participants have completed their visits at Week 48 and Week 96, respectively, and after all Extension switch participants (Section 9.3.1.6) have completed the Week 124 visit. 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 and study 201585. An ad-hoc review of data by the IDMC will be triggered whenever the number of CVFs (Section 5.4.4) in the CAB LA + RPV LA arm 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 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.

201584 is conducted in parallel with study 201585 with the aim to pool data generated from the current study with study 201585, 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-1 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 after randomization into the Maintenance Phase. 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 will be made at a one-sided 2.5% level of significance. Treatment with CAB LA + RPV LA will be declared non-inferior to continued ABC/DTG/3TC if the upper end of a two-sided 95% confidence interval for the difference between the two groups (CAB LA + RPV LA – ABC/DTG/3TC) 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 CMH weights. All CIs will be two-sided and the analysis will be stratified according to the Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) 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 HIV-1 RNA 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 LA + RPV LA treated participants, m_k is the number of ABC/DTG/3TC 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 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.

Proportion of participants with plasma HIV-1 RNA <200 c/mL and <50 c/mL, and HIV-1 RNA ≥200 c/mL and ≥50 c/mL, respectively, over time will be summarized using the Snapshot algorithm.

Proportion of participants with confirmed virologic failure will also be summarized over time.

Secondary analyses of efficacy data will include a repeat of the primary snapshot analysis of virologic failure and virologic success, as detailed above, at Week 96.

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

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

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

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

Changes from Baseline in laboratory (including fasting lipids) and vital signs data will be summarized. Vital signs at Day 1 will be summarized. In addition, the number and percentage of participants with graded laboratory toxicities (based on DAIDS categories) will be summarized by treatment group.

Change from Baseline in renal and bone biomarkers will be summarized by treatment and visit.

9.4.2.1. Week 124 Extension Switch Analysis

For the Week 124 Extension Switch population analysis (Section 9.3.1.6), antiviral response will be assessed according to the proportion of participants with and without oral lead-in, respectively, who have HIV-1 RNA ≥50 c/mL at Week 124 (i.e., 24 weeks from initiation of CAB LA + RPV LA, ±6 week analysis window, using the FDA Snapshot algorithm), with corresponding 95% confidence interval. The primary efficacy endpoint of interest for this analysis is the proportion of participants without oral lead-in who have HIV-1 RNA ≥50 c/mL at Week 124. No formal statistical comparison with respect to safety and efficacy outcomes will be performed.

Proportion of participants with plasma HIV-1 RNA <200 c/mL and <50 c/mL and confirmed virologic failure, respectively, over time will be summarized.

Absolute values and change from Extension Baseline CD4+ cell count will be summarized over time.

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

Changes from Extension Baseline in laboratory (including fasting lipids) and vital signs data will be summarized. In addition, the number and percentage of participants with Extension emergent graded laboratory toxicities (based on DAIDS categories) will be summarized by treatment group.

Further details for secondary efficacy, 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).

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.

9.4.4. 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.

9.4.5. Viral Genotyping/Phenotyping Analyses

- The incidence of treatment emergent genotypic and phenotypic resistance will be summarized by treatment arm for subjects meeting confirmed virologic failure criteria (Section 5.4.4). Details of the analyses to be performed will be specified in the reporting and analysis plan (RAP).

9.4.6. 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).

9.4.7. 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 including Week 48 and Week 96 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 and Week 96 will also be summarized by subgroups. Additional details on subgroup analyses will be provided 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 in the Maintenance Phase. 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 Healthcare/GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with 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:

- 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 any under a 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.
- Signed informed consent must be obtained for each participant prior to participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- ViiV Healthcare/GSK will provide full details of the above procedures, either verbally, in writing, or both.

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.

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 Committee

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 4.2.8 and the IDMC charter, which is available upon request.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

3TC	Lamivudine, EPIVIR
201584	FLAIR (First Long-Acting Injectable Regimen
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
ACCEPT	Chronic Treatment Acceptance questionnaire
ABC/DTG/3TC	Abacavir/dolutegravir/lamivudine, TRIUMEQ
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	Acetaminophen
API	Active pharmaceutical ingredient
ARV	Antiretroviral
ART	Antiretroviral therapy
ATV	Atazanavir
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-τ)	Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state)
BP	Blood pressure
BUN	Blood urea nitrogen
CAB	Cabotegravir
CAB LA	Cabotegravir long-acting
CABG	Coronary artery bypass grafting
c/mL	Copies/milliliter
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
CYP3A	Cytochrome P450 3A
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic acid
DRE	Disease-Related Events
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
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
ETR	Etravirine
EU	European Union
EVG	Elvitegravir
FC	Fold change
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle Stimulating Hormone
FTC	Emtricitabine
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
HAT-QoL	HIV/AIDS-targeted quality of life
HBc	Hepatitis B core antibody
HbsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HIVTSQ	HIV treatment satisfaction questionnaire
HIVTSQc	HIV treatment satisfaction questionnaire (change version)
HIVTSQs	HIV treatment satisfaction questionnaire (status version)
HLA	Human leukocyte antigen
HLA-B	Major Histocompatibility Complex, Class I, B
HR	Heart Rate
HRQL	Health-related quality of life
HSR	Hypersensitivity reaction

HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IN	Integrase
INI	Integrase inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection Site Reactions
ITT-E	Intent-to-treat Exposed
ITT-ME	Intent-to-treat Maintenance Exposed
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LA	Long acting
LDH	Lactate Dehydrogenase
LDL	Low density lipoprotein
LLOD	Lower Limit Of Detection
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MAA	Marketing Application Authorization
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mg/dL	Milligram per deciliter
MHRA	Medicines and Healthcare products Regulatory Agency
m-ITT	modified Intent to Treat
MSD=F	Missing, switch, or discontinuation equals failure
MSDS	Master Safety Data Sheet
ng/mL	Nanogram per millileter
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRS	Numeric Rating Scale
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed case
OLE	Study Name for: Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression
PA IC90	Protein adjusted 90% inhibitory concentration

PBMC	Peripheral Blood Mononuclear Cell
PI	Protease inhibitor
PI	Prediction interval
PIN	Perception of iNjection questionnaire
PI/r	Ritonavir-Boosted Protease Inhibitor
PK	Pharmacokinetic
PP	Per-protocol
PrEP	Pre-Exposure Prophylaxis
PRO	Protease
PRTD	Proximal renal tubule dysfunction
PSRAE	Possible suicidality-related adverse event
PT	Prothrombin Time
PTCA	Percutaneous transluminal coronary angioplasty
PTI	Partial Thromboplastin Time
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QTc	Corrected QT interval
RAL	Raltegravir
RAMOS NG	Randomization and Medication Ordering System Next Generation
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RBP	Retinol binding protein
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RPV	Rilpivirine, Edurant
RPV LA	Rilpivirine long-acting
RT	Reverse transcriptase
RTV, r	Ritonavir
SAE	Serious adverse event
SF	Short form survey
SJS	Stevens-Johnson syndrome
SOC	Standard of care
SPM	Study Procedures Manual
STR	Single tablet regimen
TAF	Tenofovir alafenamide
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
Tmax	Time to maximum concentration
TMC278	Tibotec Medicinal Compound 278
TSQ	Treatment Satisfaction Questionnaire
ULN	Upper limit of normal
UGT	Glucuronosyltransferase
US	United States
USP	United States pharmacopeia

VAPI	Vaccines' Perception of Injection
VAS	Visual Analog Scale
VSLC	ViiV Safety and Labeling Committee
WBC	White blood cell
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM/KIVEXA
TIVICAY
TRIUMEQ
TRIZIVIR
ZIAGEN

Trademarks not owned by the ViiV Healthcare
Edurant
GenoSure
Genvoya
Monogram Biosciences
PhenoSense
Stribild

12.2. Appendix 2: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Averse Events 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 LIFE-THREATENING
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-THREATENING
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	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 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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 *Report only one* *> 16 years of age*	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
≤ 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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipoatrophy [4]	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
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 indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, 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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 interventi on other than iron suppleme nt	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 indicated	Life-threatening consequences (e.g., circulatory failure, 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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to 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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 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 *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

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 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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 bronchospasm	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 indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
2 to 5 years of age	NA	WHO Weight-for-height z-score < -2 to ≤ -3	WHO Weight-for- height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	NA	WHO Weight-for-length z-score < -2 to ≤ -3	WHO Weight-for- length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
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, 2007 reference tables may be accessed 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 dysfunction	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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 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 treatment	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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
≤ 28 days of age	NA	NA	NA	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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)* *≥ 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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 CKD-EPI and Schwatrz in mL/min/1.73m^2).
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[3] (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*) *> 7 days of age*	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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
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 (male and female)	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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
INR, High (not on anticoagulation therapy)	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 therapy)	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 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy)	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
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
17. Male and female sex are defined as sex at birth. 18. 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 dipstick)	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 indicated	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.tech-res.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 subject 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 15, 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 16, 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)

- subject 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 (Table 15, Figure 9)**:**

- Principal Investigator (PI) requests consideration of drug rechallenge for a subject receiving ***compelling benefit from a critical or life-saving drug***, who exhibits liver chemistry elevation meeting subject 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 subject's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and ***complete checklist*** **(**Table 15**)**.
- 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 subject 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)
    - Subject 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:

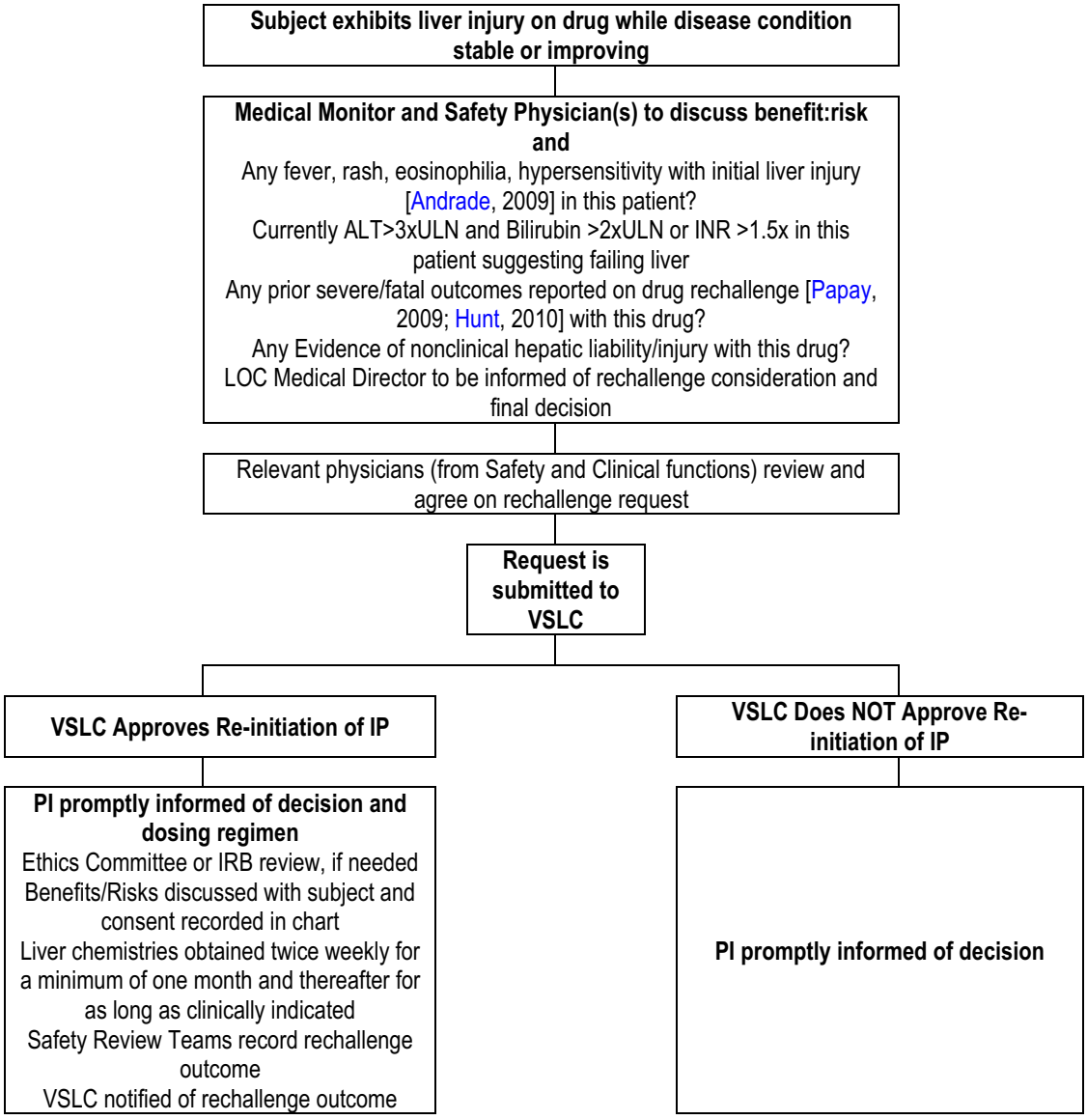
- Safety Review Team Leader, Safety Development Leader, or Senior Safety Physician
- Medicines Development Leader (MDL) and Project Physician Leader (PPL)

- Request is taken to full VSLC for final decision.

Table 15 **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 subject 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)		
Subject 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.

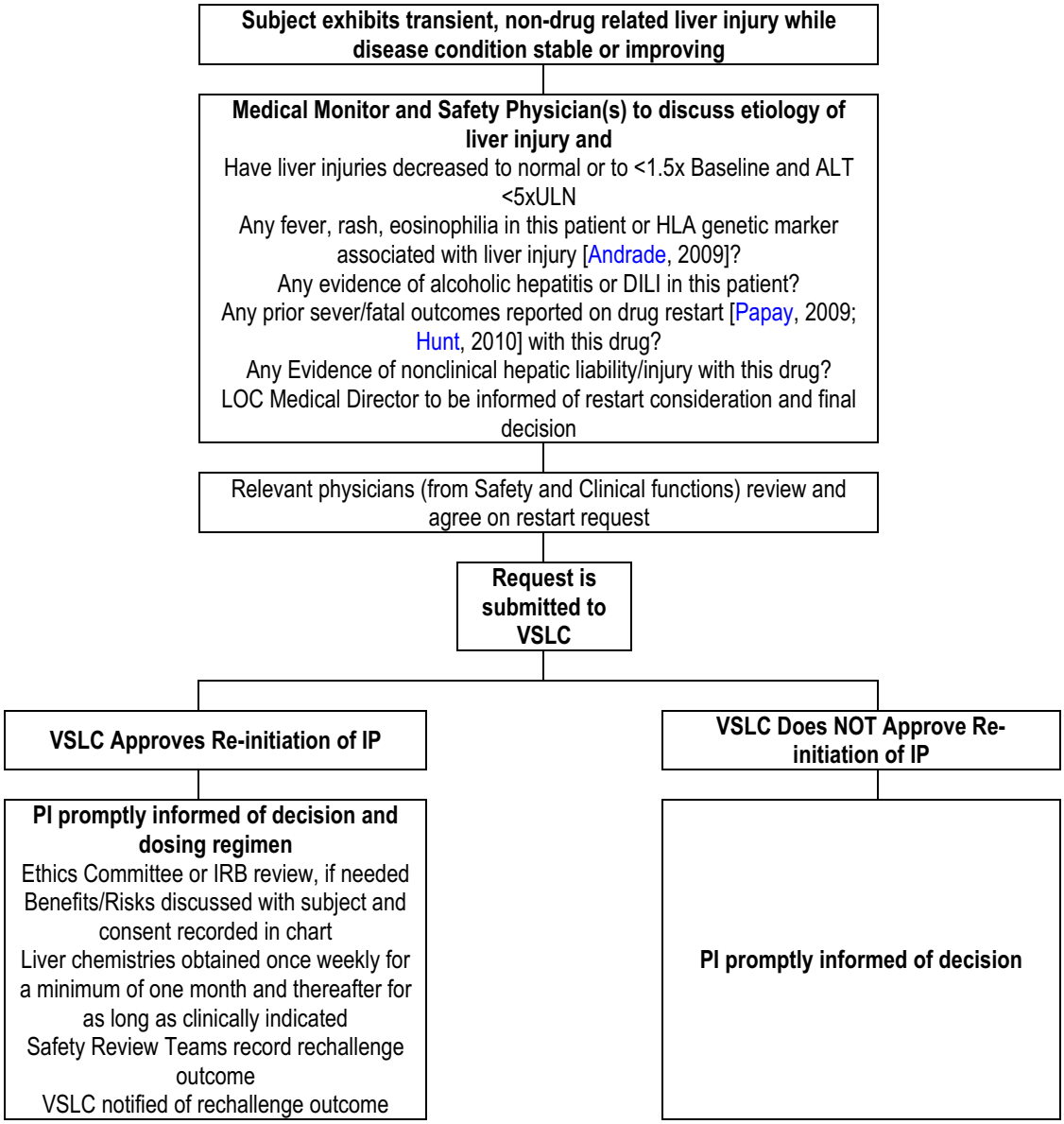
VSLC DECISION PROCESS FOR DRUG RESTART APPROVAL OR DISAPPROVAL

- **Principal Investigator (PI) requests consideration of drug re-initiation for a subject stable or improving on IP, who exhibits liver chemistry elevation meeting subject 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 subject's diagnosis restart risk factors (Hepatotoxicity Panel consultation is available) and complete checklist (Table 16).
  - ***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 16 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 subject 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 subject 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#	Subject#	Rechallenge or Restart?	Safety outcome*	Drug benefit

Rechallenge/restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting subject stopping criteria
- 2 = recurrent liver chemistry elevation meeting subject stopping criteria
- 3 = serious adverse event
- 4 = fatality

12.4. Appendix 4: CDC Classification System for HIV-1 Infections (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 the relationship between genetic variants and:

- Response to medicine, including CAB + RPV, ABC/DTG/3TC, or any concomitant medicines;
- HIV-1 infection 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 Reporting and Analysis Plan (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 subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the 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 subject has been enrolled 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 subject 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 subject 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.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject 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 subject 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 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 subject 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 subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject 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 Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject'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 subject, 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 <u>NOT</u> 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 subject'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 subject'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:

a. Results in death

b. 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.

c. 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.

d. 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
e. Is a congenital anomaly/birth defect
f. 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
g. 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.
• Refer to Appendix 3 for the required liver chemistry follow-up instructions

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 eCRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.6.6. Reporting of SAEs to ViiV Healthcare / GSK

SAE reporting to ViiV Healthcare / GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to ViiV Healthcare / 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.

12.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

a. Premenarchal

b. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.7.1. Contraception Guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 17.

Table 17 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Two highly effective methods of contraception should be utilized from 30 days prior to the first dose of study medication, throughout the study, and for at least 52 weeks after discontinuation of CAB LA and RPV LA .

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed as per the study Time and Events Table.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing will be performed and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert.

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. 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.
- 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 Appendix 6. 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 participant who becomes pregnant while participating will discontinue study medication and be withdrawn from the study. If the participant is receiving CAB LA + RPV LA, they will be followed for 52 weeks in the Long-Term Follow-Up Phase.

12.8. Appendix 8: Country Specific Requirements

12.8.1. United Kingdom (UK)

This requirement has been included based on requests from the Medicines and Healthcare products Regulatory Agency (MHRA) to include information on the specific duration of the Extension or Continuation Phase/Study Treatment for similar Phase 3 trials.

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. For participants in the UK, estimating a 6 month recruitment period, Marketing Application Authorisation (MAA) submission in 1-2Q2019, and 14 to 15 months approval time for the MAA, the Extension Phase is anticipated to conclude by approximately 2-3Q2020. During this time, participants will be monitored every 4 weeks to ensure they continue to derive clinical benefit from CAB LA + RPV LA.

12.8.2. Japan

Pharmacokinetics

For Japanese participants in the study, blood samples for CAB will be taken at the visit shown in the following table in addition to the visits scheduled in Table 5 of Section 7.1 (Time and Event Table) in the protocol.

Table 18 Additional PK Visit and Sample Times for Japanese Participants

Day	Time (Related to Dosing of Study agent)
Oral Cabotegravir	
Day 1 (following first oral dose during lead-in phase)	Pre-dose, 1, 2, 3, 4, 8, and 24 hours post-dose

The total, maximum, amount of blood drawn for PK during this entire study is approximately 146 mL for Japanese participants.

Plasma concentration-time data on Day 1 and Week 4b in Japanese participants will be analyzed by non-compartmental methods with WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, pharmacokinetic parameters (e.g. Cmax, AUC, tmax, *etc*) will be determined, as data permit. Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively as appropriate. Plasma concentration levels of the drug from this study will be also evaluated using a population pharmacokinetics model.

Full details of all summaries and analyses will be included in the RAP.

12.9. Appendix 9: Protocol Amendments

12.9.1. Amendment 01 (All Countries)

PROTOCOL AMENDMENT RATIONALE

The rationale for this amendment includes changes to the following: added new primary Medical Monitor contact information; added lipid objective and endpoint back in to the table within the Synopsis section; added clarification of text for patient reported outcome endpoints; added additional clarification regarding provision of CAB LA and RPV LA until available through public/government health sectors; new text added to allow use of local labs to determine eligibility in exceptional circumstances; updated Time and Events Table to provide more clarity around assessments conducted during the Extension Phase, added 'X' to include collection of cardiovascular risk information at Screening, added temperature to Vital Signs row, added row for randomization, and clarified timings for completion of patient reported questionnaires relative to other clinical assessments in the table footnotes; clarified timing of dosing for abacavir/dolutegravir/lamivudine (ABC/DTG/3TC, Triumeq) for the Day 1 visit; added additional clarification that participants of child bearing potential must continue contraception for at least 52 weeks after the last injection; revised text to say that Investigators may provide 'bridging' supply after consultation with Medical Monitor (vs Medical Monitor authorizing bridging supply); provided clarification that cabotegravir and rilpivirine exposure may persist for more than one year in some participants after intramuscular administration (with added references); minor edits to prohibited medication information; added statement that drugs that cause Torsade de Pointes should be used with caution when taking rilpivirine; additional clarification that background NRTI therapy is not considered Investigational Product and accountability will not be done for NRTI background; changed film coat color for Tivicay (dolutegravir) from white (clinical trial material supply) to yellow (commercial supply) and removed statement to "protect from light" (for both Triumeq and Tivicay); sentence added for collection of additional details for the injection device used for IM administration; additional information included regarding randomization schedule; added text stating the investigator must discuss long-term commitment for the study with potential participants; added statement regarding serofast RPR results; allowed serum pregnancy testing where required locally (e.g. when urine testing is not available); removed duplicate text regarding monitoring for suicidal related events; added option for patient reported outcomes to be collected on paper instrument if needed; removed information in Appendix requiring collection of pregnancy information for female partners of male study participants; definition of ACCEPT, HIVTSQc, and HIVTSQs added to abbreviations table, duplication of ICH abbreviation removed; other minor corrections (e.g., updated references, adding cross reference to sections, correction of hyperlink to one table).

New text is bolded below (Table headings and bolded text within the existing document may also appear in bold font). Deleted text has strikethrough in original text field, or is noted as 'deleted text'.

PROTOCOL CHANGES / CLARIFICATIONS

Medical Monitor/Sponsor Information Page

Rationale: Updated Medical Monitor information page to include contact information for new Medical Monitor:

Original Text:

Primary Medical Monitor/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

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

Revised Text:

Primary Medical Monitor/SAE Contact Information:

PPD **DO, MSc**
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, 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

Sponsor Serious Adverse Events (SAE) Contact Information:

PPD **DO, MSc**
ViiV Healthcare
Research Triangle Park
Five Moore Drive, Research Triangle Park, NC 27709 (USA)
Mobile: PPD
Office Telephone: PPD
Fax: PPD
e-mail: PPD

Section 1 Protocol Synopsis; Objective/Endpoints:

Rationale: Secondary lipid endpoint and objective inadvertently left out of synopsis table (included in Section 3. Objective and Endpoints)

Added Text:

Objectives	Endpoints
To evaluate the effects of CAB LA + RPV LA every 4 weeks on fasting lipids over time compared to continuation of ABC/DTG/3TC over time.	• **Change from Baseline in fasting lipids over time including Week 48 and Week 96.**

Section 1 Protocol Synopsis; Objective/Endpoints AND Section 3 Objectives and Endpoints:

Rationale: Clarification provided for Health Outcomes Endpoints

Original Text:

Objectives	Endpoints
To assess the acceptance of pain and injection site reactions following injections.	• Dimension scores (e.g., "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). • 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 treatment satisfaction of CAB LA + RPV LA compared to continuation of ABC/DTG/3TC.	• 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 degree of health-related quality of life (HR QoL) ~~using the HIV/AIDS-targeted quality of life (HAT-QoL) questionnaire short form~~.	• ~~Summary statistics and between and within treatment group comparisons of c~~hange in HR QoL ~~from Day 1 and~~ Week 24, Week 48, Week 96 (or Withdrawal).
To assess ~~the~~ health status ~~using the 12-item Short Form Survey (SF-12)~~.	• ~~Summary statistics and between and within treatment group comparisons of c~~hange in health status ~~from Day 1 and~~ Week 24, Week 48, and Week 96 (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 c~~hange in treatment acceptance ~~(using the ACCEPT) from Day 1 and~~ Week 8, Week 24, Week 48, Week 96 (or Withdrawal).

Objectives	Endpoints
To assess tolerability of injections ~~using the Numeric Rating Scale (NRS) for participants randomized to the CAB + RPV LA arm~~.	• ~~Summary statistics and within treatment group comparisons and c~~hange in tolerability of injection ~~from Week 4b,~~ Week 5, Week 40, Week 41, and Week 96.

Revised Text:

Objectives	Endpoints
To assess the acceptance of pain and injection site reactions following injections.	• **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).
To assess treatment satisfaction of CAB LA + RPV LA compared to continuation of ABC/DTG/3TC.	• Change from baseline in total "treatment satisfaction" score, and **individual item scores** of the **HIV Treatment Satisfaction Questionnaire (status version)** (HIVTSQs) **at Week 4b, Week 24, Week 44, Week 96 (or Withdrawal).** • Change in treatment satisfaction over time (using the HIVTSQ **change version [HIVTSQc]**) at Week 48 (or Withdrawal).
To assess degree of health-related quality of life (HR QoL).	• **C**hange **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 health status.	• **C**hange **from Baseline** in health status **at** Week 24, Week 48, and Week 96 (or

Objectives	Endpoints
	Withdrawal) **using the 12-item Short Form Survey (SF-12).**
To assess treatment acceptance.	• **C**hange **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.	• **C**hange **from Week 4b** in tolerability of injection**s at** Week 5, Week 40, Week 41, and Week 96 **using the Numeric Rating Scale (NRS) within the CAB LA + RPV LA arm.**

Section 1 Protocol Synopsis: Overall Design;
Section 1 Treatment Arms and Duration (both Induction and Maintenance Phase Sections);
Section 4.1 Overall Design;
Section 4.2.2 Induction Phase;
Section 4.2.3, Maintenance Phase (Day 1 to Week 100); and
Section 6.3 Dose and Administration:

Rationale: New text added providing clarification of timing of Day 1 dose relative to randomization.

New Text Added:

ABC/DTG/3TC dosing on Day 1 should 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 ABC/DTG/3TC prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1.

Section 1 Protocol Synopsis, Long-Term Follow-Up Phase – IM Regimen Only and Section 4.2.6. Long-Term Follow-Up Phase – IM Regimen Only

Rationale: Clarification added that adequate contraception must be used for at least 52 weeks (rather than stating throughout the entire year of follow-up):

Original Text:

Female participants of child bearing potential must continue to use adequate contraception methods for ~~the entire year of follow-up~~.

Revised Text:

Female participants of child bearing potential must continue to use adequate contraception methods for **at least 52 weeks after the last injection**.

Section 1 Protocol Synopsis, Protocol Permitted Substitutions, and Section 6.8.1 Oral Bridging

Rationale: Text revised to state Investigators may provide bridging supply following consultation with the Medical Monitor (vs Medical Monitor authorizing bridging supply)

Original Text:

Following the Induction Phase, 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.

Revised Text:

Following the Induction Phase, in exceptional circumstances, **and in consultation with the Medical Monitor, Investigators may provide** oral CAB and RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA **and who will miss a subsequent scheduled LA injection**. 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 4.2.1. Screening Phase

Rationale: New text added to allow use of local labs to determine eligibility in exceptional circumstances.

New Text Added:

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. Similarly, if a central laboratory result cannot be generated for genotype/phenotype, a local result can be considered following review and approval by the study virologist.

Section 4.2.3. Eligibility for the Maintenance Phase – Text Slightly Revised and Moved to Section 4.2.4. Maintenance Phase (Day 1 to Week 100)

Rationale: Text is referring to potential safety issues while a participant is taking oral CAB and RPV, which will not be administered until Day 1 of the Maintenance Phase.

Original Text:

~~In addition to the viral load criteria above,~~ if in the opinion of the Investigator, a participant experiences a significant safety event while taking either CAB or RPV, Maintenance eligibility will be determined ONLY in consultation with the Medical Monitor. Any rash that is possibly related to study drug, and is present between Day 1 and Week 4b, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA (See Section 7.4.5.13).

Revised Text:

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 between Day 1 and Week 4b, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA (See Section 7.4.5.13).

Section 4.2.5.1. Participants Entering from the CAB LA + RPV LA Arm

Rationale: Added additional clarification regarding provision of CAB LA and RPV LA until available through public/government health sectors.

Original Text:

All participants who successfully complete 100 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 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.

Revised Text:

All participants who successfully complete 100 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 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.

Section 4.2.5.2. Participants Entering from the ABC/DTG/3TC Arm

Rationale: Clarification that labs must be reviewed before the Week 104b visit.

Original Text:

In addition, central lab results and safety parameters from the Week 104a visit must be available and reviewed.

Revised Text:

In addition, central lab results and safety parameters from the Week 104a visit must be available and reviewed **before the Week 104b visit**.

Section 4.6.1. Risk Assessment

Rationale: Clarification that CAB and RPV can have residual concentrations beyond 1 year.

Original CAB Text:

Development of Resistance following discontinuation of CAB LA	Residual concentrations of CAB would remain in the systemic circulation of participants for prolonged periods (~~up to~~ 1 year) 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.

Revised CAB Text:

Development of Resistance following discontinuation of CAB LA	Residual concentrations of CAB would remain in the systemic circulation of participants for prolonged periods **(more than 1 year in some participants; GlaxoSmithKline Document Number 2016N269422_00; Study 201120)** 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.

Original RPV Text:

Development of Resistance	Residual concentrations of RPV would remain in the systemic circulation of participants who stopped treatment (e.g. for tolerability issues or treatment failure) ~~for prolonged periods (months)~~. 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 four weeks after participants stop RPV LA. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimizing of 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.

Revised RPV Text:

Development of Resistance	Residual concentrations of RPV can remain in the systemic circulation of participants who stopped treatment (e.g. for tolerability issues or treatment failure) **for more than one year in some participants [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 four weeks after participants stop RPV LA. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimizing of 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.

Section 4.6.1. Risk Assessment, CAB Table

Rationale: allowance of short term glucocorticoids use changed from 14 days to 21 days within CAB table.

Original Text:

Drug-Drug Interactions (DDIs)	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.

Revised Text:

Drug-Drug Interactions (DDIs)	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 5.1. Inclusion Criteria:

Rationale: New text added to allow use of local labs to determine eligibility in exceptional circumstances.

New Text Added:

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. Similarly, if a central laboratory result cannot be generated for genotype/phenotype, a local result can be considered following review and approval by the study virologist.

Section 5.2. Exclusion Criteria #21:

Rationale: Short term corticosteriod use modified to 21 days, further clarified this exemption is related to chronic (vs short term use).

Original Text:

Immunomodulators that alter immune responses (such as systemic corticosteroids, interleukins, or interferons). Note: Participants using short-term (e.g. ≤~~14~~ day) systemic corticosteroid treatment, topical, inhaled or intranasal corticosteroids, are eligible for enrollment.

Revised Text:

Immunomodulators that alter immune responses (such as **chronic** systemic corticosteroids, interleukins, or interferons). Note: Participants using short-term (e.g. **≤21** day) systemic corticosteroid treatment**;** topical, inhaled or intranasal corticosteroids, are eligible for enrolment.

Section 6.1. Investigational Product and Other Study Treatment

Rationale: Provided clarification that dual NRTI to be taken with single entity DTG is not considered IP.

Original Text:

In this study, investigational product (IP) refers to oral ABC/DTG/3TC (or alternate DTG + NRTI background therapy), oral CAB, and CAB LA, which will be supplied by GlaxoSmithKline and oral RPV and RPV LA which will be supplied by Janssen Pharmaceuticals.

Revised Text:

In this study, investigational product (IP) refers to oral ABC/DTG/3TC single tablet regimen (or alternately DTG), oral CAB, and CAB LA, which will be supplied by GlaxoSmithKline and oral RPV and RPV LA which will be supplied by Janssen Pharmaceuticals. The dual NRTI background therapy that is administered with single entity DTG is not considered IP.

Section 6.1.5. ABC/DTG/3TC STR – Tablet

Rationale: Removed statement to 'protect from light' as this is not a storage requirement for ABC/DTG/3TC.

Original Text:

ABC/DTG/3TC tablets are to be stored at 25°C [77°F] (excursions permitted to 15°-30°C [59°-86°F])~~ and protected from light~~.

Revised Text:

ABC/DTG/3TC tablets are to be stored at 25°C [77°F] (excursions permitted to 15°-30°C [59°-86°F]).

Section 6.1.6. Dolutegravir – Tablet

Rationale: Film coat color changed from white (clinical trial material [CTM] color) to yellow (commercial supply color), sentence removed that the film coat was the only difference between CTM and commercial supply, and statement removed to 'protect from light'.

Original Text:

Dolutegravir is manufactured by GlaxoSmithKline and will be provided to participants who are *HLA-B*5701* positive (to be used in combination with 2 NRTIs). DTG 50 mg tablets are ~~white~~, round, biconvex, film-coated tablets. The tablets contain 52.62 mg dolutegravir sodium salt, which is equivalent to 50 mg dolutegravir free acid. Each tablet is debossed with "SV 572" on one side and "50" on the other side. ~~The tablets are the same formulation as the commercial material with the exception of the film coat color.~~ The tablets are packaged into high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each bottle contains 30 tablets and a desiccant. DTG tablets are to be stored at 25°C [77°F] (excursions permitted to 15°-30°C [59°-86°F]) ~~and protected from light.~~

Revised Text:

Dolutegravir is manufactured by GlaxoSmithKline and will be provided to participants who are *HLA-B*5701* positive (to be used in combination with 2 NRTIs). DTG 50 mg tablets are yellow, round, biconvex, film-coated tablets. The tablets contain 52.62 mg dolutegravir sodium salt, which is equivalent to 50 mg dolutegravir free acid. Each tablet is debossed with "SV 572" on one side and "50" on the other side. The tablets are packaged into high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each bottle contains 30 tablets and a desiccant. DTG tablets are to be stored at 25°C [77°F] (excursions permitted to 15°-30°C [59°-86°F]).

Section 6.2. Treatment Assignment:

Rationale: Text added to describe the randomization schedule and the benefit of central randomization to eliminate selection bias.

New Text:

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. Dose and Administration (in addition to text noted above regarding changes to Day 1 ABC/DTG/3TC dosing)

Rationale: Clarification to dosing table regarding timing of Day 1 ABC/DTG/3TC dosing and that Induction Phase is Week [-20] to (vs through) Day 1.

Original Text:

Induction Phase (Week [-20] ~~through~~ Day 1) – All Subjects	
Week (-20) to Day 1 (1 tablet once daily)	Take 1 tablet ABC 600 mg / DTG 50 mg / 3TC 300 mg once daily *with or without food*

And

ABC/DTG/3TC Once Daily Arm*	
Day 1 to Week 100 (1 tablet once daily)	Take 1 tablet ABC 600 mg / DTG 50 mg / 3TC 300 mg once daily *with or without food*

Revised Text:

Induction Phase (Week [-20] to Day 1) – All Subjects	
Week (-20) to Day 1 (1 tablet once daily)	Take 1 tablet ABC 600 mg / DTG 50 mg / 3TC 300 mg once daily *with or without food* ***Take Day 1 dose after randomization.***

And

ABC/DTG/3TC Once Daily Arm*	
Day 1 to Week 100 (1 tablet once daily)	Take 1 tablet ABC 600 mg / DTG 50 mg / 3TC 300 mg once daily *with or without food* ***Take Day 1 dose after randomization.***

Section 6.3. Dose and Administration

Rationale: deleted text regarding how often IP was taken (with a meal) on average, as this is not recorded in the eCRF.

Deleted Text:

The participant will be asked how often the IP was taken (with a meal) on average, since the last visit, and this information will be recorded in the eCRF.

Section 6.6. Preparation/Handling/Storage/Accountability

Rationale: clarification added that accountability will not be done for NRTI background therapy taken with single entity DTG.

Original Text:

IP accountability will be evaluated using pill counts of unused IP for participants receiving oral treatment (ABC/DTG/3TC [or alternate DTG ~~+ NRTIs~~], oral CAB, oral RPV). ~~This assessment~~ will be conducted each time the participant receives a new/refill supply of IP, when the participant completes oral CAB and RPV (including oral bridging supply), and through the Withdrawal visit, study completion, or Week 104b of the Extension Phase.

Revised Text:

IP accountability will be evaluated using pill counts of unused IP for participants receiving oral treatment (ABC/DTG/3TC [or alternate DTG], oral CAB, oral RPV). **Pill counts will not be done for the dual NRTIs taken with DTG, as these will not be provided centrally. IP accountability** will be conducted each time the participant receives a new/refill supply of IP, when the participant completes oral CAB and RPV (including oral bridging supply), and through the Withdrawal visit, study completion, or Week 104b of the Extension Phase.

Section 6.6.1. Dosing Considerations for CAB LA + RPV LA

Rationale: Added statement to allow collection of more information on injection device..

New Text: 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

Rationale: Provided clarification that pill counts will not be done for NRTIs taken with single entity DTG, that start and stop dates will be recorded in the eCRF, and that Investigators should discuss the long-term commitment for the study with the participants and have counselling plans in place for both treatment arms.

Original Text:

IP accountability will be evaluated using pill counts of unused IP (CAB and RPV tablets at the end of oral dosing [including bridging supply], and ABC/DTG/3TC [or alternate DTG ~~+ NRTIs~~]). This assessment will be conducted each time the participant receives a supply of oral study medication. These data will be recorded in the participant's eCRF.

When participants are dosed with CAB LA and RPV LA at the site, they will receive IM injections directly from the investigator or designee, under medical supervision. The date

and time of each injection of CAB LA and RPV LA administered in the clinic will be recorded in the source documents. These data 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.

IP accountability will not be assessed during the Long-Term Follow-Up Phase.

Due to the long acting nature of the CAB LA and RPV LA, it will be imperative that the participant is compliant with dosing visits.

Investigators must have plans in place for adherence counselling.

Revised Text:

IP accountability will be evaluated using pill counts of unused IP (CAB and RPV tablets at the end of oral dosing [including bridging supply], and ABC/DTG/3TC [or alternate DTG]). This assessment will be conducted each time the participant receives a supply of oral study medication. These data will be recorded in the participant's eCRF. **Treatment start and stop dates will also be recorded in the eCRF.**

When participants are dosed with CAB LA and RPV LA at the site, they will receive IM injections directly from the investigator or designee, under medical supervision. The date and time of each injection of CAB LA and RPV LA administered in the clinic will be recorded in the source documents. These data 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.

IP accountability **(e.g. pill counts)** will not be assessed **for alternate NRTIs taken with single entity DTG**, or during the Long-Term Follow-Up Phase.

Due to the long acting nature of the CAB LA and RPV LA, it will be imperative that the participant is compliant with dosing visits. **As part of the screening and participant selection process, Investigators must discuss with potential participants the long-term commitments for the study, and the importance of adhering to treatment regimens.**

Investigators must have plans in place for adherence counselling **for both treatment arms.**

Section 6.9.1. IM Dosing

Rationale: clarification that both LA drugs may have measurable plasma concentrations beyond 1 year, and reiterated the need for HAART as concentrations decline over time.

Original Text:

Participants receiving CAB LA and~~/or~~ RPV LA are anticipated to be at high 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 drugs may be measurable for ~~approximately 52 weeks~~ following IM injections.

Revised Text:

Participants receiving CAB LA and RPV LA are anticipated to be at high 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 in some participants** 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 (e.g. in the Long-Term Follow-Up Phase) to minimize the risk of developing resistance as concentrations of CAB and RPV decline over time.**

Section 6.13. Concomitant Medications and Non-Drug Therapies; Oral RPV administration Only

Rationale: Added drugs that may cause TdP should be used with caution during the study when taking rilpivirine.

New Text:

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

Section 6.13.1. Prohibited Medications and Non-Drug Therapies

Rationale: Removed restricted duration for topical imiquimod as minimal systemic exposure is expected (other than maintaining [‘short term use’], changed duration for glucorticoid use to 21 days to allow, e.g., for treatment of pneumocystis pneumonia, clarified HCV treatment is also prohibited during Induction. Corrected typo in glucocorticoids.

Original Text:

- 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.

- Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis (James, 2009).
- 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 t~~opical, 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 is prohibited throughout the entire study. Options for treatment of hepatitis C should be discussed with the Medical Monitor prior to initiation of therapy.

Revised Text:

- 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. **U**se of topical imiquimod is permitted.
- Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis (James, 2009).
- Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided due to **the** 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, **but** more than a single dose **in a treatment course** may cause **a** significant decrease in RPV plasma concentration and is prohibited. **T**opical, inhaled or intranasal use of glucocorticoids will be allowed.
- Hepatitis C infection therapy is prohibited during the **Induction and** Maintenance Phase before the Week 48 primary endpoint, and interferon-based HCV therapy is prohibited throughout the entire study. Options for treatment of hepatitis C should be discussed with the Medical Monitor prior to initiation of therapy.

Section 6.13.1. Prohibited Medications and Non-Drug Therapies: Concurrent with RPV

Rationale: Clarification added that local prescribing information for oral RPV should be reviewed for drugs that 'are prohibited' with RPV as the list within the protocol may not be as current as local prescribing information.

Original Text:

Please refer to the local prescribing information for other drugs that should be used with caution, require dose adjustment, or increased clinical monitoring if taken with oral RPV.

Revised Text:

Please refer to the local prescribing information for other drugs that **are prohibited,** should be used with caution, require dose adjustment, or increased clinical monitoring if taken with oral RPV.

Section 7.1. Time and Events Table

Rationale: New text added before table to explain visits and assessments during the Extension Phase.

New Text Added Before Table:

Beginning at Week 112, the schedule of assessments for participants continuing in the Extension Phase from the CAB LA + RPV LA arm will be modified to collect clinical chemistries, HIV-1 RNA, and CD4+ cell count every 12 weeks.

Participants originally randomized to ABC/DTG/3TC at Day 1, who choose to continue into the Extension Phase and transition to CAB LA + RPV LA, will have all assessments noted in the Time and Events table below performed Q4W from Week 108 through Week 124. Beginning at Week 124, the schedule of assessments for these participants transitioning from ABC/DTG/3TC into the Extension Phase will be modified to collect clinical chemistries, HIV-1 RNA, and CD4+ cell count every 12 weeks as noted in the Time and Events schedule below.

From Week 124 forward, all participants (from both originally randomized treatment arms), will have the same schedule of events (same visits, same assessments, same time frame).

Changes to Time and Events Table (see Section 7.1 for example):

- Row added for randomization at Day 1
- Cardiovascular Risk Assessment: "X" noted at Screening
- Temperature added to Vital Signs row
- PK row – Clarified S = Storage sample
- Study treatment accountability – Corrected footnote in column for Week 104b to reflect footnote 'u' instead of footnote 'v'.
- Column added for assessments performed Q4W after Week 108 (LA Arm) or after Week 124 (Switch Arm)
- Column for Q12W assessments in Extension renamed to clarify assessments begin at W112 (LA Arm) and W124 (Switch Arm)

- Footnote 'i' regarding eCSSR completion clarifies that this assessment should be the last patient reported outcome assessment completed (still completed at the beginning of the visit).
- Footnote 'j' changed to allow serum pregnancy testing if required locally: "**Serum pregnancy test can substitute for urine pregnancy test if locally required, but must be appropriately timed to confirm pregnancy status prior to e.g randomization and first IM administration.**"
- Footnote 's' symbol removed from Week 104b column and "- LA Arm Only" added to column
- Footnote 'z' deleted reference to "PIN" questionnaire, added that patient reported assessments should be completed prior to eCSSRs assessments, and changed to include completion of health outcomes questionnaires at withdrawal if prior to Week 96 (vs Week 48).
- Footnote aa: "NRS" questionnaire added to first sentence, e.g. The PIN, Preference, **and NRS** questionnaires are to be administered only to participants receiving CAB LA + RPV LA injections. The NRS should be collected 30 to 60 minutes post-injection (and at Week 5 and Week 41, one week post-injections)

Section 7.2.1. Screening

Rationale: New text added to allow use of local labs to determine eligibility in exceptional circumstances. Additionally, text deleted regarding Screening labs available prior to 'randomization' (earlier statement in preceeding paragraph explains that all Screening labs must be available prior to 'enrollment'[e.g., Week -20]).

Original Text:

Laboratory results from the central laboratory services provided by this trial will be used to assess study eligibility. A single repeat of a procedure / lab parameter is allowed to determine eligibility (unless otherwise specified). ~~All Screening labs **must** be available prior to randomization.~~

Each participant screened will be assigned a participant number. Participants not meeting all inclusion and exclusion criteria at initial screen may be re-screened one time with a new participant number. Participants who are enrolled into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

At Screening, samples for HIV-1 genotypic and phenotypic resistance testing and plasma HIV-1 RNA measurement will be obtained.

Revised Text:

Laboratory results from the central laboratory services provided by this trial will be used to assess study eligibility. 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.

Each participant screened will be assigned a participant number. Participants not meeting all inclusion and exclusion criteria at initial screen may be re-screened one time with a new participant number. Participants who are enrolled into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

At Screening, samples for HIV-1 genotypic and phenotypic resistance testing and plasma HIV-1 RNA measurement will be obtained. **If a central laboratory result cannot be generated for Screening genotype/phenotype, a local result can be considered following review and approval by the study virologist.**

Section 7.2.1. Screening

Rationale: Clarification added that HBV DNA will only be performed for participants with positive anti-HBc and negative HBsAg and negative anti-HBs.

Original Text:

HBV DNA will only be performed for participants with ~~both~~ anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).

Revised Text:

HBV DNA will only be performed for participants with **positive** anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).

Section 7.2.1. Screening

Rationale: Additional information included regarding participants with a serofast RPR result.

New Text:

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.

Section 7.4.1. Clinical Evaluations

Rationale: Clarification of temperature collection.

New Text:

Temperature will also be collected.

Section 7.4.1. Clinical Evaluations

Rationale: Added allowance for serum pregnancy testing to replace urine testing if locally required.

New Text:

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).

Section 7.4.2. Laboratory Assessments

Rationale: Footnote 'g' added to Table to address when HBV DNA will be performed (previously stated in Section 7.2.1. Screening). Footnote letters within the table updated to include this addition.

New Text:

g. HBV DNA will only be performed for participants with a positive anti-HBc, negative HBsAg, and negative anti-HBs (past and / or current evidence).

Section 7.4.3.4.

Rationale: Link provided to sections for reporting cardiovascular and death events.

New Text:

Additional information for reporting cardiovascular and death events is included in Section 7.4.3.7. and Section 7.4.3.8., respectively.

Section 7.4.6. Suicidal Risk Monitoring

Rationale: Duplicate Text Removed

Original Text:

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.

Revised Text:

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.

Section 7.4.6. Suicidal Risk Monitoring

Rationale: Added text to ensure sites have a plan for managing risk of and possible suicide related events.

New Text:

All sites should have a plan in place for managing risk of and possible suicide related events.

Section 7.5.1. PK Sample Collection

Rationale: Added clarification regarding visits windows and sample collection windows, and added 20 to 28 hour window for pre-dose samples at Week 4b and Week 104b.

Original Text:

PK window for sample collection: Pre-dose ***visits***: ±3 days (1st injection), minus 7 days (2nd and 3rd injection), and± 7days (4th and all subsequent injections), 2 hours post dose: ±one hour; one week post dose visits: 3 to 10 days post injection.

Revised Text:

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± 7 days (4th and all subsequent injections); **Sample Collection: Pre-dose at Week 4b (and Week 104b for participants transitioning from ABC/DTG/3TC 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

Rationale: Added option of paper instrument collection if needed, and clarified timing of NRS assessment:

Original Text:

Health outcomes assessments will be conducted according to the Time and Events Table (Table 5). Assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments.

Revised Text:

Health outcomes assessments will be conducted according to the Time and Events Table (Table 5). 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)

Rationale: Additional clarification provided for patient reported outcome analyses.

Original Text:

- Dimension scores (e.g., "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).

- 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 ~~"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).

- ~~Summary statistics and between and within treatment group comparisons will be assessed on c~~hange in treatment acceptance ~~from Day 1 (using the ACCEPT) and~~ Weeks 8, 24, 48, 96 (or Withdrawal from the study).

- ~~Summary statistics and between and within treatment group comparisons will be assessed in the broader impact on health status (using the SF-12) from Day 1, and Weeks 24, 48, 96 (or Withdrawal from the study).~~

- ~~Summary statistics and between and within treatment group comparisons will be asses on c~~hange in HR QoL (using the HAT-QoL short form) ~~from Day 1~~, Weeks 24, 48, 96 (or Withdrawal from the study).

- ~~Summary statistics and within treatment group comparisons will be assessed on~~ the tolerability of injections (using the NRS) at Weeks 4b, 5, 40, 41, 96 ~~on participants randomized to the "CAB LA and RPV LA" arm. Change in tolerability of injection will be assessed from Week 4b and Week 48 (primary analysis), and from Week 4b and Week 96 (secondary analysis).~~

Revised Text:

- **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 Week 4b, Week 24, Week 44, Week 96 (or Withdrawal)**.

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

- **C**hange **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.**

- **C**hange **from Baseline in health status at Weeks 24, 48, 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** the tolerability of injections (using the NRS) at Weeks 5, 40, 41, 96.

Section 12.7.2. Collection of Pregnancy Information

Rationale: Bullets regarding collecting information for female partner (of male study participants) who become pregnant while participating in the study were deleted. CAB is characterized as low risk for teratogenicity or genotoxicity on the basis of available non-clinical data, and therefore, in the 201584 study, there are not plans to monitor pregnancies outcomes in female partners of male subjects, consistent with GSK standard operating procedures. There is also a statement within inclusion criteria number two that 'ALL subjects participating in the study must be counseled on safer sexual practices to minimize risk of HIV transmission.' While there is an expectation that men taking part in the study will practice safe sex, it is not being monitored as part of the study.

Removed 'female' in statement describing follow-up for participants who become pregnant while on LA treatment.

Original Text:

Any ~~female~~ 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.

- ~~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.~~

Revised Text:

Any participant who becomes pregnant while participating will discontinue study medication and be withdrawn from the study. If the participant is receiving CAB LA + RPV LA, they will be followed for 52 weeks in the Long-Term Follow-Up Phase.

ADMINISTRATIVE CORRECTIONS (E.G. TYPOGRAPHICAL ERRORS, NEW REFERENCES)

Throughout document:

Rationale: Corrected typo in "enrolment" (vs "enrollment")

Section 4.2.8. Independent Data Monitoring Committee

Rationale: clarification that IDMC will review 201584 and 201585, and corrected typo with "of of".

Original Text:

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.

An IDMC will evaluate accumulating efficacy, tolerability / safety, and PK of ~~of~~ CAB LA + RPV LA at predetermined times during the study.

Revised Text:

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 **(201584)** and study 20158**5.**

An IDMC will evaluate accumulating efficacy, tolerability / safety, and PK of CAB LA + RPV LA at predetermined times during the study.

Section 5.4.1.2. Liver Event Adjudication Committee

Rationale: Added "be" to the following statement:

A liver safety panel will **be** used to evaluate all subjects who meet liver stopping criteria. Uniform sets of data and standards for adjudication will be applied across cases to inform outcomes.

Section 5.4.5.1. HIV-1 RNA Blips

Rationale: Corrected typo in "scheduled"

Original Text:

Following discussion with the Medical Monitor, additional viral load testing may be performed between visits to determine the appropriate participant disposition for the next ~~secheduled~~ visit (e.g. if additional injections should be administered).

Revised Text:

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 (e.g. if additional injections should be administered).

Section 7.4.2. Laboratory Assessments – typo corrected for labelled (vs labeled).

Section 9.2.1. Sample Size Assumptions – hyperlink corrected in second paragraph from Table 10 to Table 13, e.g., 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).

Section 11. References

Rationale: Added references for CAB and RPV exposures beyond 1 year in some participants.

New Text:

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). Durban, South Africa. Abstract TUAC0103.

Section 11. References

Rationale: Updated Reference for Hunt CM 2010 and added ICH E2 Reference.

Revised (bolded) / New Text:

Hunt CM. **Mitochrondrial and Immunoallergic Injury Increase Risk of Positive Drug Rechallenge After Drug-Induced Liver Injury: A Systematic Review.** *Hepatol* 2010;52:2216-2222.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline; Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. 27Oct1994. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

Section 12.1 Appendix 1: Abbreviations and Trademarks

The following abbreviations were added to the table:

ACCEPT	Chronic Treatment Acceptance questionnaire
HIVTSQc	HIV treatment satisfaction questionnaire (change version)
HIVTSQs	HIV treatment satisfaction questionnaire (status version)

The following row was deleted the from the table (2 rows with ICH abbreviation):

ICH	International Conference on Harmonisation Harmonisation Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Section 12.2 Appendix 2: Division of AIDS Table – the following typo was corrected: (Medical intervention vs Medicamylasal intervention)

Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medica~~mylasal~~ intervention indicated	Posterior or pan- uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)

Section 12.3 Appendix 3 Liver Safety – Study Treatment Restart or Rechallenge

"Table" was entered twice in the following sentence (first instance of "Table" has been deleted:

- **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 subject 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**~~ Table 14, Figure 9).

12.9.2. Amendment 02 (All Countries)

Protocol changes for Amendment 02 (19-JUL-2017), from amendment 01 (13-DEC-2016)

PROTOCOL AMENDMENT RATIONALE

The rationale for this amendment includes: update of contact information for secondary Medical Monitor; modify text to allow dose reduction for participants who have a decline in creatinine clearance to <50 mL/min; clarify that for participants not eligible to continue into the Maintenance Phase, only samples with HIV-1 RNA > 400 c/mL will be sent for resistance testing; add mitigation for ECG pad removal; clarify ± 3 day window is for all oral dosing (both Induction and Maintenance Phase); add "LA Arm" back to columns for Week 68, 76, 84, 92 on Time and Events Schedule (hidden when column was narrowed); clarify Week 104b visit is specific to those participants transitioning from oral IP to CAB LA + RPV LA; clarification added to footnote 'p' that genetics sample can be collected at any visit after signing informed consent, but the Week [-20] visit is preferred; correct footnote on Week 5 visit to reflect footnote 't'; add footnote 'y' back to Time and Events column for Withdrawal Visit (for Induction Phase); add clarification to Time and Events column that ISR assessments are only conducted for subjects receiving injections. Administrative typographical errors corrected (e.g. clarification provided regarding genetics sample taken after participants are enrolled into the study [vs when

participants are randomized]), and investigator brochure references updated, references added.

PROTOCOL CHANGES / CLARIFICATIONS

Medical Monitor/Sponsor Information Page

Rationale: Updated phone contact information for secondary Medical Monitor:

Original Text:

Secondary Medical Monitor:

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

New Text:

Secondary Medical Monitor:

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

Section 1: PROTOCOL SYNOPSIS, Protocol Permitted Substitutions

Rationale: Clarification provided that dose reduction for lamivudine is allowed for participant's with creatinine clearance <50 mL/min (consistent with prescribing information).

Original Text:

….. Local prescribing information should be consulted for information regarding use of these medications.

Following the Induction Phase, in exceptional circumstances, and in consultation with the Medical Monitor, Investigators may provide oral CAB and RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA and who will

miss a subsequent scheduled LA injection. 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.

~~No other dose reductions, modifications, or changes in the frequency of any components of any regimen will be allowed during the Maintenance and Extension Phases of the study.~~

Revised Text:

….. Local prescribing information should be consulted for information regarding use of these medications.

For consistency with prescribing information, dose reductions of lamivudine (or emtricitabine if used as alternate NRTI) are permitted as needed for creatinine clearance <50 mL/min throughout the study. No other dose reductions, modifications, or changes in the frequency of any components of any regimen will be allowed during the Maintenance and Extension Phases of the study.

Following the Induction Phase, in exceptional circumstances, and in consultation with the Medical Monitor, Investigators may provide oral CAB and RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA and who will miss a subsequent scheduled LA injection. 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 4.2.3. Eligibility for the Maintenance Phase

Rationale: Clarification provided that only samples with HIV-1 RNA >400 c/mL at Week -4 will be resent for resistance testing.

Original Text:

If the participant is ineligible for the Maintenance Phase, samples will be sent to a central laboratory for resistance testing and results provided to the Investigator once available.

Revised Text:

If the participant is ineligible for the Maintenance Phase, samples **with a HIV-1 RNA >400 c/mL** will be sent to a central laboratory for resistance testing and results provided to the Investigator once available.

Section 4.2.7. Dose Modifications / Permitted Treatment Substitutions

Rationale: Clarification provided that dose reduction for lamivudine is allowed for participant's with creatinine clearance <50 mL/min (consistent with prescribing information).

Original Text:

During the Induction Phase, prior to randomization into the Maintenance Phase at Day 1, one switch to an alternate approved background NRTI therapy is allowed for toxicity or tolerability management. The date of a decision to switch the NRTI background therapy for toxicity or tolerability management must be documented in the eCRF. Switches of a background NRTI for any other reason are not permitted in the study. Local prescribing information should be consulted for information regarding use of these medications.

A short term bridging supply for participants on the CAB LA + RPV LA arm may be permitted following discussion with the Medical Monitor (see Section 6.8.1.). No other dose reductions, modifications, or changes in the frequency of any components of any regimen will be allowed during the Maintenance and Extension Phases of the study.

Revised Text:

During the Induction Phase, prior to randomization into the Maintenance Phase at Day 1, one switch to an alternate approved background NRTI therapy is allowed for toxicity or tolerability management. The date of a decision to switch the NRTI background therapy for toxicity or tolerability management must be documented in the eCRF. Switches of a background NRTI for any other reason are not permitted in the study. Local prescribing information should be consulted for information regarding use of these medications.

A short term bridging supply for participants on the CAB LA + RPV LA arm may be permitted following discussion with the Medical Monitor (see Section 6.8.1.).

For consistency with prescribing information, dose reductions of lamivudine (or emtricitabine if used as alternate NRTI) are permitted in the context of renal insufficiency (throughout the study), e.g. as needed for creatinine clearance <50 mL/min.

If a dose reduction of lamivudine, a component of TRIUMEQ, is required for participants with creatinine clearance less than 50 mL/min, the individual entities should be used (e.g. DTG tablets, ABC tablets, 3TC tablets as separate medications, with dosing consistent with prescribing information). DTG can be provided centrally through the study. Single entity products will need to be sourced locally and can be reimbursed by the Sponsor as needed. Lamivudine (3TC) dose reduction will be allowed throughout the study, and is not considered to be a "switch to an alternative approved background NRTI therapy", but rather an alignment with prescribing information to maintain consistent 3TC plasma exposure for participants with renal insufficiency.

No other dose reductions, modifications, or changes in the frequency of any components of any regimen will be allowed during the Maintenance and Extension Phases of the study.

Section 4.6.1. Risk Assessment; Table, Study Procedures

Rationale: Added mitigation for ECG pad removal.

Original Text:

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.**

Revised Text:

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.	• ECGs will be conducted by appropriately trained personnel and effort made to minimise contact time for application of the pads.

Section 5.4. Withdrawal/Stopping Criteria

Rationale: Clarification provided that dose reduction for lamivudine is allowed for participant's with creatinine clearance <50 mL/min (consistent with prescribing information).

Original Text:

- Participant requires a second switch or a dose adjustment of any component of the ABC/DTG/3TC. A substitution for NRTI backbone is allowed at Screening, e.g. ABC/3TC to TDF/FTC or TAF/FTC for participants who are *HLA-B*5701* positive. During the Induction Phase, prior to randomization into the Maintenance Phase at Day 1, one switch to an alternate approved background NRTI therapy is allowed for toxicity or tolerability management.

Revised Text:

- Participant requires a second switch or a dose adjustment of any component of the ABC/DTG/3TC **(with exception of dose reduction for renal insufficiency as noted in Section 4.2.7.)**. A substitution for NRTI backbone is allowed at Screening, e.g. ABC/3TC to TDF/FTC or TAF/FTC for participants who are *HLA-B*5701* positive. During the Induction Phase, prior to randomization into the Maintenance

Phase at Day 1, one switch to an alternate approved background NRTI therapy is allowed for toxicity or tolerability management.

Section 6.8. Protocol Permitted Substitutions

Rationale: Clarification provided that dose reduction for lamivudine is allowed for participant's with creatinine clearance <50 mL/min (consistent with prescribing information).

New Text Added:

For consistency with prescribing information, dose reductions of lamivudine (or emtricitabine if used as alternate NRTI) are permitted throughout the study in the context of renal insufficiency, e.g. as needed for creatinine clearance <50 mL/min (See Section 4.2.7. for additional information).

Section 6.9.2. Oral Dosing

Rationale: Clarification that ± 3 day window applies to all oral dosing in Induction, Maintenance, and Extension Phases of the study.

Original Text:

There is a (+ or -) 3 day visit window, from the projected visit date.

Revised Text:

There is a (+ or -) 3 day visit window, from the projected visit date **(for all oral dosing in the Induction, Maintenance, and Extension Phases of the study)**.

Section 7.1. Time and Events Table

Rationale: Columns and Footnotes updated that were accidently deleted with Amendment 1.

Corrections made:

- 'y' footnote added back to WD column for Induction Phase. Also added the word 'oral' to clarify this is a follow-up visit for participants withdrawing from oral IP (participants withdrawing from CAB LA + RPV LA will go into Long-Term Follow-Up).
- clarification added to footnote 'p' that genetics sample can be collected at any visit after signing informed consent, but the Week [-20] visit is preferred;
- Week 5 footnote corrected to letter 't' (vs 's').
- 'LA Arm' added back to column for Weeks 68, 76, 84, 92 (hidden when column was narrowed).
- Week 104b – clarification that this visit is only required for the participants switching from oral to LA.

ADMINISTRATIVE CORRECTIONS (E.G. TYPOGRAPHICAL ERRORS, UPDATED REFERENCES)

Section 11. References (Also updated in Section 4.6 and Section 5.0)

Rationale: Updated investigator brochure references to include most recent version numbers.

Original Text:

GlaxoSmithKline Document Number RH2009/00003/~~05~~: GSK1265744 (Cabotegravir) Clinical Investigator's Brochure, Version ~~05~~, ~~January~~ 2016.

Revised Text:

GlaxoSmithKline Document Number RH2009/00003/**06**: GSK1265744 (Cabotegravir) Clinical Investigator's Brochure, Version **06**, **December** 2016.

Original Text:

Rilpivirine Clinical Investigator Brochure [RPV IB], April ~~2016~~.

Revised Text:

Rilpivirine Clinical Investigator Brochure [RPV IB], **Edition Number 10**, April **2017**.

Section 11.0. References

Rationale: Added references identified in DAIDS table to Reference Section.

New Text:

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.

New Text:

World Health Organization (WHO) Growth Reference: Available at http://www.who.int/growthref/who2007_bmi_for_age/en/.

Section 12.5. Appendix 5: Genetic Research, Study Assessments and Procedures

Rationale: Clarification that samples are collected after participant's are 'enrolled' versus 'randomized.'

Original Text:

A blood sample is collected at the baseline visit, after the subject has been ~~randomized~~ and provided informed consent for genetic research.

Revised Text:

A blood sample is collected at the baseline visit, after the subject has been **enrolled** and provided informed consent for genetic research.

Section 12.9.1. Amendment 01 (All Countries)

Rationale: Correction made to rationale section to be consistent with protocol text regarding 52 weeks of contraception required (vs 52 years).

Original Text:

Section 1 Protocol Synopsis, Long-Term Follow-Up Phase – IM Regimen Only and Section 4.2.6. Long-Term Follow-Up Phase – IM Regimen Only

Rationale: Clarification added that adequate contraception must be used for at least 52 ~~years~~ (rather than stating throughout the entire year of follow-up):

Revised Text:

Section 1 Protocol Synopsis, Long-Term Follow-Up Phase – IM Regimen Only and Section 4.2.6. Long-Term Follow-Up Phase – IM Regimen Only

Rationale: Clarification added that adequate contraception must be used for at least 52 **weeks** (rather than stating throughout the entire year of follow-up):

12.9.3. Amendment 03 (All Countries)

Protocol changes for Amendment 03 (25-JUN-2018), from amendment 02 (19-JUL-2017)

PROTOCOL AMENDMENT RATIONALE

Changes for Amendment 3 were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defect in infants born to women with exposure to dolutegravir (DTG) at the time of conception.

- A Risk Assessment table was added to include language regarding risk and mitigation of neural tube defects seen with DTG.
- The withdrawal criteria were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant should also be withdrawn from the study.
- The Time and Events table was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy.

Additionally, clarifications were provided for the following:

- the DTG IB should be referenced for additional risks, safety information, drug interactions, etc.;
- 'suspected' was added to the text prior to the bulleted definition of suspected virologic failure in Section 5.4.5.3.;
- specific storage conditions were removed from the protocol for IP, and a statement added to store according to product label;
- insulin was removed from the section regarding clinical assessments performed during the study;
- timeframe for pregnancy reporting and follow-up were updated to 24 hours to align with current reporting process;
- prescribing information and IB references were updated.

PROTOCOL CHANGES / CLARIFICATIONS

Section 4.6 Benefit:Risk Assessment

Rationale: DTG IB added as reference for benefit/risk profile (and typos corrected)

Original Text:

ABC/DTG/3TC is established regimen that has been in clinical use for several years and has ~~well~~ an established benefit/risk profile described in detail in the respective country product labels (TRIUMEQ Prescribing Information, 201~~5~~).

Revised Text:

ABC/DTG/3TC is **an** established regimen that has been in clinical use for several years and has an established benefit/risk profile described in detail in the **DTG IB (GlaxoSmithKline Document Number RM2007/00683/11**) **and** respective country product labels (TRIUMEQ Prescribing Information, 201**8**).

Section 4.6 Benefit:Risk Assessment

Rationale: New text adding regarding risk of neural tube defects associated with DTG:

New Text:

A potential safety issue related to neural tube defect in infants born to women with exposure to dolutegravir (DTG) at the time of conception has been recently identified as noted below:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [ABC/DTG/3TC, DTG] Refer to DTG IB and country product labels for additional information		
DTG: Neural tube defects	**In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.**	**1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, 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) from 30 days prior to the first dose of study medication 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.** **2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded;** **3. Women who become pregnant, or who desire to be pregnant while in the study will have study treatment discontinued and withdrawn from the study.** **4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit.** **5. Pregnancy status is monitored at every study visit.**

Section 5 Selection of Study Population and Withdrawal Criteria

Rationale: DTG IB added as reference.

Original Text:

Information for ABC/DTG/3TC or DTG is provided in the US or country product label (TRIUMEQ Prescribing Information, 201~~5~~; TIVICAY Prescribing Information, 201~~5~~).

Revised Text:

Information for ABC/DTG/3TC or DTG is provided in the **current DTG IB (GlaxoSmithKline Document Number: RM2007/00683/11) and** US or country product label (TRIUMEQ Prescribing Information, 201**8**; TIVICAY Prescribing Information, 201**7**).

Section 5.4. Withdrawal/Stopping Criteria

Rationale: Reminder added to withdraw participants from the study if they desire to become pregnant or who are no longer willing to comply with contraceptive requirements.

New Text:

As a reminder, females of reproductive potential who changed their minds and desire to be pregnant, or who state they are no longer willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.

Section 5.4.5.2. Suspected Virologic Failure

Rationale: "suspected" added to the paragraph directing investigators to obtain confirmation of virologic failure.

Original Text:

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

Revised Text:

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

Section 6.1.1. Cabotegravir (CAB) – Tablet

Rationale: Storage conditions removed from text and direction provided to refer to the product label.

Original Text:

CAB tablets are to be stored ~~up to 30°C [86°F] and protected from moisture~~.

Revised Text:

CAB tablets are to be stored **according to the product label.**

Section 6.1.2. Rilpivirine (RPV) – Tablet

Rationale: Storage conditions removed from text and direction provided to refer to the product label.

Original Text:

RPV tablets should be stored ~~at 25°C (excursions permitted to 15°-30°C [59°-86°F]) and protected from light~~.

Revised Text:

RPV tablets are to be stored **according to the product label.**

Section 6.1.3. Cabotegravir – Injectable Suspension (CAB LA)

Rationale: Storage conditions removed from text and direction provided to refer to the product label.

Original Text:

CAB LA injectable suspension is to be stored ~~at up to 30°C, do not freeze~~.

Revised Text:

CAB LA injectable suspension is to be stored **according to the product label.**

Section 6.1.4. Rilpivirine – Injectable Suspension (RPV LA)

Rationale: Storage conditions removed from text and direction provided to refer to the product label.

Original Text:

RPV LA injectable suspension ~~should be kept in the outer package and stored at 2-8°C (do not freeze)~~. ~~RPV LA~~ should ~~also~~ be protected from light.

Revised Text:

RPV LA injectable suspension should be stored **according to the product label and** should be protected from light.

Section 6.1.5. ABC/DTG/3TC STR - Tablet

Rationale: Storage conditions removed from text and direction provided to refer to the product label.

Original Text:

ABC/DTG/3TC tablets are to be stored ~~at 25°C [77°F] (excursions permitted to 15°-30°C [59°-86°F])~~.

Revised Text:

ABC/DTG/3TC tablets are to be stored **according to the product label**.

Section 6.1.6. Dolutegravir (DTG) - Tablet

Rationale: Storage conditions removed from text and direction provided to refer to the product label.

Original Text:

DTG tablets are to be stored ~~at 25°C [77°F] (excursions permitted to 15°-30°C [59°-86°F])~~.

Revised Text:

DTG tablets are to be stored **according to the product label.**

Section 6.13. Concomitant Medications and Non-Drug Therapy

Rationale: Added use of investigator brochure to evaluate potential drug:drug interactions.

Original Text:

The investigator should evaluate any potential drug:drug interactions at every visit, including reviewing the most current version of the U.S and/or local prescribing information for RPV, and ABC/DTG/3TC (or DTG + NRTIs), especially if any new concomitant medications are reported by participants.

Revised Text:

The investigator should evaluate any potential drug:drug interactions at every visit, including reviewing the most current version of **the investigator brochures**, the U.S and/or local prescribing information for RPV, and ABC/DTG/3TC (or DTG + NRTIs), especially if any new concomitant medications are reported by participants.

Section 6.13.1. Prohibited Medications and Non-Drug Therapies

Rationale: Added use of investigator brochure to evaluate potential drug:drug interactions.

Original Text:

For additional information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy used during the study (e.g. ABC/DTG/3TC), please consult and local prescribing information.

Revised Text:

*For additional information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy used during the study (e.g. ABC/DTG/3TC), please consult **the current DTG Investigator brochure** and local prescribing information.*

Original Text (Concurrent with RPV):

Please refer to local prescribing information for other drugs that are prohibited, should be used with caution, require dose adjustment, or increased clinical monitoring if taken with oral RPV.

Revised Text:

*Please refer to **the current RPV Investigator brochure** and local prescribing information for other drugs that are prohibited, should be used with caution, require dose adjustment, or increased clinical monitoring if taken with oral RPV.*

Original Text (Concurrent with ABC/DTG/3TC):

Please refer to the local prescribing information for other drugs that should be used with caution, require dose adjustment, or increased clinical monitoring if taken with ABC/DTG/3TC (or DTG with alternate NRTI background therapy).

Revised Text:

*Please refer to the **current DTG IB and** local prescribing information for other drugs that should be used with caution, require dose adjustment, or increased clinical monitoring if taken with ABC/DTG/3TC (or DTG with alternate NRTI background therapy).*

Original Text (Concurrent with DTG + 2 NRTIs):

In addition to the prohibited medications noted for DTG above (as a component of ABC/DTG/3TC), for participants who are *HLA-B*5701* positive and who are receiving DTG + alternate NRTI background therapy, refer to local prescribing information for details regarding concurrent therapies.

Revised Text:

In addition to the prohibited medications noted for DTG above (as a component of ABC/DTG/3TC), for participants who are *HLA-B*5701* positive and who are receiving DTG + alternate NRTI background therapy, refer to **the current DTG IB and** local prescribing information for details regarding concurrent therapies.

Section 7.1. Time and Events Table

Rationale: Reminder added to footnote 'j' to avoid pregnancy while on study and to adhere to contraceptive requirements.

Original Text:

j. Conduct pregnancy tests for only women of childbearing potential at every visit throughout the study, including Q4W during the Extension Phase. A negative urine pregnancy test is required prior to beginning the Induction Phase (Week [-20]), on Day 1 (preferably prior to randomization), and at Week 4b (or Week 104b for subjects transitioning from ABC/DTG/3TC) prior to the first injection. Serum pregnancy test can substitute for urine pregnancy test if locally required, but must be appropriately timed to confirm pregnancy status prior to e.g. randomization and first IM administration. S=Serum/U=Urine.

Revised Text:

j. Conduct pregnancy tests for only women of childbearing potential at every visit throughout the study, including Q4W during the Extension Phase. **Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.** A negative urine pregnancy test is required prior to beginning the Induction Phase (Week [-20]), on Day 1 (preferably prior to randomization), and at Week 4b (or Week 104b for subjects transitioning from ABC/DTG/3TC) prior to the first injection. Serum pregnancy test can substitute for urine pregnancy test if locally required, but must be appropriately timed to confirm pregnancy status prior to e.g. randomization and first IM administration. S=Serum/U=Urine.

Section 7.4.1. Clinical Evaluations

Rationale: Removed insulin as a periodic assessment, as this was not collected for 201584.

Original Text:

- Periodic assessment of glucose, ~~insulin,~~ and bone and renal markers**.**

Revised Text:

- Periodic assessment of glucose, and bone and renal markers**.**

Section 7.4.3.4. Prompt Reporting of Serious Adverse Events and Other Event (Text and Table 7) – Pregnancy Reporting Row

Rationale: Updated timeframe for pregnancy reporting and follow-up.

Original Text:

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 ~~2 weeks~~ of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

Revised Text:

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. The investigator should inform GSK within **24 hours** of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

Original Table Row:

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**
Pregnancy	~~2 weeks~~	"Pregnancy Notification Form"	~~2 weeks~~	"Pregnancy Follow-up Form"

Revised Table Row:

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**
Pregnancy	**24 hours**	"Pregnancy Notification Form"	**Within 24 hours of investigator awareness of pregnancy outcome**	"Pregnancy Follow-up Form"

Section 7.4.7.3. Action to be Taken if Pregnancy Occurs

Rationale: Updated timeframe for pregnancy reporting.

Original Text:

~~To ensure participant safety, if a pregnancy is reported then~~ the investigator should inform GSK within ~~2 weeks~~ of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

Revised Text:

The investigator should inform GSK within **24 hours** of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

Section 12.7.2. Collection of Pregnancy Information

Rationale: Updated timing for collection of pregnancy information.

Original Text:

- Information will be recorded on the appropriate form and submitted to GSK within ~~2 weeks~~ of learning of a participant's pregnancy.

Revised Text:

- Information will be recorded on the appropriate form and submitted to GSK within **24 hours** of learning of a participant's pregnancy.

ADMINISTRATIVE CORRECTIONS (E.G., UPDATED REFERENCES)

Section 11: References

Original Text:

Edurant Prescribing Information, ~~August~~ ~~2015~~.

Revised Text:

Edurant Prescribing Information, **February 2018**.

Original Text:

GlaxoSmithKline Document Number RH2009/00003/0~~6~~: GSK1265744 (Cabotegravir) Clinical Investigator's Brochure, Version 0~~6~~, December ~~2016~~.

Revised Text:

GlaxoSmithKline Document Number RH2009/00003/0**7**: GSK1265744 (Cabotegravir) Clinical Investigator's Brochure, Version 0**7**, December **2017**.

Original Text:

GlaxoSmithKline Document Number RM2007/00683/~~09~~: GSK1349572 Clinical Investigator's Brochure, Version ~~09~~, ~~09~~ October ~~2015~~.

Revised Text:

GlaxoSmithKline Document Number RM2007/00683/**11**: GSK1349572 Clinical Investigator's Brochure, Version **11**, **13** October **2017**; **Supplement 01, 11 Dec 2017; Supplement 02, Jun 2018**.

Original Text:

TIVICAY Prescribing Information, ~~August 2015~~.

Revised Text:

TIVICAY Prescribing Information, **November 2017**.

Original Text:

TRIUMEQ Prescribing Information, ~~September 2015~~.

Revised Text:

TRIUMEQ Prescribing Information, **May 2018**.

12.9.4. Amendment 04 (All Countries)

Protocol changes for Amendment 04 (24-SEP-2018), from Amendment 03 (25-JUN-2018). Some of the modifications noted below are not inclusive of full text within a section, but rather the edited pieces of the section.

PROTOCOL AMENDMENT RATIONALE

The primary reason for protocol amendment 04 is to allow an optional (vs mandatory) oral lead-in for participants randomized to the ABC/DTG/3TC arm who choose to continue into the Extension Phase of the study and receive CAB LA + RPV LA. The Appendix (Appendix 7) for contraceptive guidance and collection of pregnancy information was updated to be consistent with current protocol template text. Other minor clarifications were made as needed, e.g., the eCSSRs timing in the footnote for the Time and Events Table, updated abbreviations, etc.

PROTOCOL CHANGES / CLARIFICATIONS

Section 1.0 Protocol Synopsis for 201584, Rationale:

Rationale for change: to highlight direct to injection as an option for participants transitioning from ABC/DTG/3TC to CAB LA + RPV LA in the Extension Phase.

Original Text:

Eligible participants (HIV-1 ribonucleic acid [RNA] <50 c/mL at Week 96) would transition to LA dosing, ~~beginning with 4 weeks oral CAB + RPV therapy at Week 100, and receive the first IM CAB LA + RPV LA injections at Week 104b~~.

Revised Text:

Eligible participants (HIV-1 ribonucleic acid [RNA] <50 c/mL at Week 96) would transition to LA dosing, beginning with the first IM CAB LA + RPV LA injections at **either Week 100 (direct to injection) or Week 104b (following optional oral lead-in with CAB 30 mg and RPV 25 mg).**

Section 1.0. Protocol Synopsis for 201584, Objectives/Endpoints AND Section 3.0. Objectives And Endpoints:

Rationale for change: an objective that was Exploratory in previous versions of the protocol has been modified to a Secondary endpoint to provide data for participants transitioning from ABC/DTG/3TC to CAB LA + RPV LA in the Extension Phase, with or without CAB + RPV oral lead-in. Secondary endpoint also added to support the importance of collecting PK data in participants who do not use an oral lead-in.

Original Text:

Exploratory	
~~To evaluate the antiviral and immunologic effects, safety and tolerability, and viral resistance of CAB LA + RPV LA for all participants in the Extension Phase.~~	• ~~Proportion of participants with plasma HIV-1 RNA <200 c/mL and HIV-1 RNA <50 c/mL over time.~~ • ~~Proportion of participants with confirmed virologic failure over time.~~

Exploratory	
	• ~~Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV in over time.~~ • ~~Absolute values and change from Baseline in plasma HIV-1 RNA over time.~~ • ~~Absolute values and changes from Baseline in CD4+ cell counts over time.~~ • ~~Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death).~~ • ~~Incidence and severity of AEs and laboratory abnormalities over time.~~ • ~~Proportion of participants who discontinue treatment due to AEs over time.~~ • ~~Absolute values and changes in laboratory parameters over time.~~

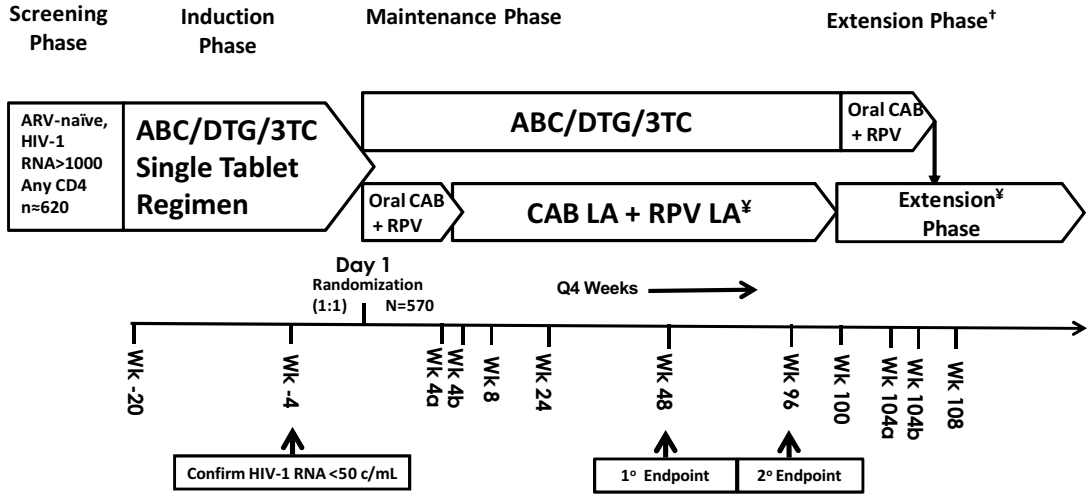
Revised Text:

Secondary	
To evaluate the antiviral and immunologic effects, safety and tolerability, and development of viral resistance to CAB LA + RPV LA at Week 124 and over time for participants switching from ABC/DTG/3TC in the Extension Phase, *with and without optional oral lead-in.*	• **Proportion of participants with HIV-1 RNA ≥ 50 c/mL at Week 124, with and without oral lead-in (FDA Snapshot algorithm, Extension Switch population).** • **Proportion of participants with plasma HIV-1 RNA <50 c/mL and HIV-1 RNA <200 c/mL over time.** • **Proportion of participants with confirmed virologic failure over time.** • **Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV over time.** • **Absolute values and change from Baseline in CD4+ cell counts over time.** • **Incidence and severity of AEs and laboratory abnormalities over time.** • **Proportion of participants who discontinue treatment due to AEs over time.** • **Absolute values and change in laboratory parameters over time.**
To evaluate the pharmacokinetics of CAB and RPV in the setting of no oral lead-in for participants switching from ABC/DTG/3TC in the Extension Phase.	• **To evaluate plasma CAB and RPV concentrations over time (Week 100 [direct to inject without oral lead-in] and Week 104 [both direct to inject and optional oral lead-in participants])**

Section 1.0. Protocol Synopsis for 201584, Overall Design AND Section 4.1. Overall Design, Study Schematic:

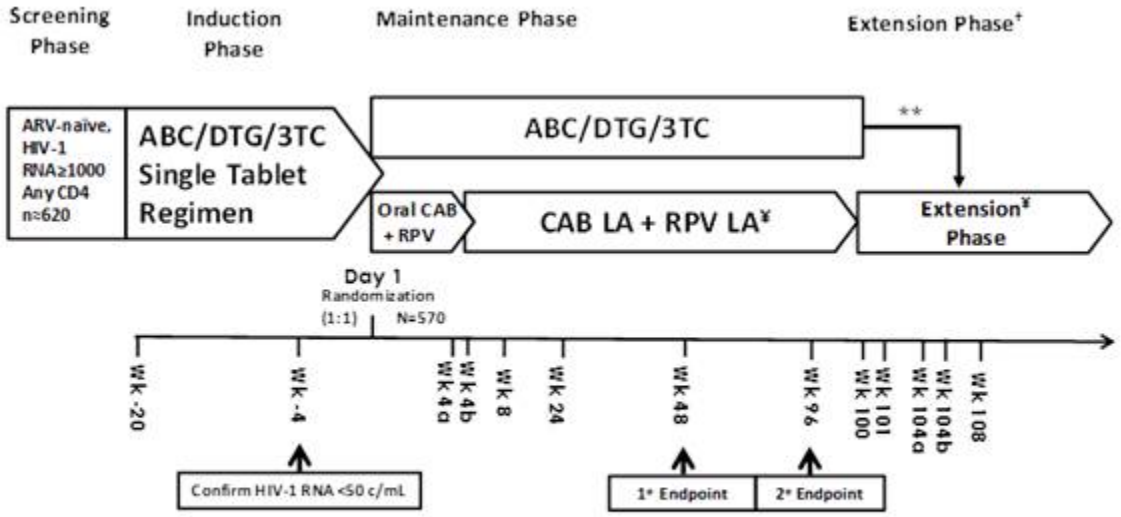
Rationale for change: to highlight direct to injection as an option for participants transitioning from ABC/DTG/3TC to CAB LA + RPV LA in the Extension Phase. Also corrected error in schematic entry viral load from >1000 c/mL to ≥1000 c/mL.

Original Text:



†Optional switch to CAB LA + RPV LA at Wk 100 for subjects randomized to ABC/DTG/3TC.
¥Subjects who withdraw from IM CAB LA + RPV LA treatment must enter the 52 week long term follow up phase.

Revised Text:



** Optional oral lead-in (investigator discretion) available from Week 100 to Week 104b

¥Subjects who withdraw from IM CAB LA + RPV LA must enter the 52 week Long Term Follow-Up Phase.

Section 1.0. Protocol Synopsis for 201584, Treatment Arms and Duration AND Section 4.2.4. Maintenance Phase (Day 1 to Week 100):

Rationale for change: to highlight patients must remain virologically suppressed through Week 96 to continue into the Extension Phase.

Original Text:

- Continue on the oral ABC/DTG/3TC initiated during the Induction Phase for at least an additional 100 weeks. Participants who successfully complete Week 100 (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.

Revised Text:

- Continue on the oral ABC/DTG/3TC initiated during the Induction Phase for at least an additional 100 weeks. Participants who successfully complete Week 100 (without meeting study defined withdrawal criteria and who remain virologically suppressed **through Week 96**: 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.

Section 1.0 Protocol Synopsis for 201584, Treatment Arms and Duration, Extension Phase:

Rationale for change: updated to reflect the two options for participants transitioning from ABC/DTG/3TC to CAB LA + RPV LA in the Extension Phase. Also rearranged some text to improve flow of section.

Original Text:

Extension Phase

Participants Entering from the CAB LA + RPV LA Arm

All participants who successfully complete Week 100 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 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~~.

Participants Entering from the ABC/DTG/3TC Arm

Participants randomized to continue ABC/DTG/3TC 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 100.

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 ABC/DTG/3TC while eligibility is being confirmed.

All participants with an undetectable HIV-1 RNA (<50 c/mL) result from the Week 96 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 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 with a 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 96 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 with a Week 96 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 100. Clinical chemistries will also be assessed ~~at Week 100~~. At Week 104a, following the 4 week CAB + RPV oral lead-in, participants will have additional safety assessments including clinical chemistries. In addition, central lab results and safety parameters from the Week 104a visit must be available and reviewed. If a clinical chemistry retest is required based on Week 104a labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 104a). Participants will remain on oral CAB 30 mg + RPV 25 mg until the Week 104b injection visit, and until any required Visit 104a retest results are available for review.

~~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.~~

~~Participants not eligible to enter the Extension Phase will end their study participation (Week 100 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.~~

Revised Text:

Extension Phase

All eligible participants who transition into the Extension Phase 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.

Participants not eligible to enter the Extension Phase will end their study participation (Week 100 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.

Participants Entering from the CAB LA + RPV LA Arm

All participants who successfully complete Week 100 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.

Visits will continue to occur every 4 weeks.

Participants Entering from the ABC/DTG/3TC Arm

Participants randomized to continue ABC/DTG/3TC 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 100.

The transition from ABC/DTG/3TC to CAB LA + RPV LA within the Extension Phase can be completed with or without an oral lead-in prior to commencement of injectable treatment. The oral lead-in decision will be made by the participant in consultation with the investigator and must be appropriately documented. As participants approach the Week 100 visit, sites must ensure sufficient CAB and RPV supply are available to support the participant's decision for transition to LA.

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 ABC/DTG/3TC while eligibility is being confirmed.

All participants with an undetectable HIV-1 RNA (<50 c/mL) result from the Week 96 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 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 with a 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 96 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 Transitioning Direct to Injection in the Extension Phase

Central lab results and safety parameters from the Week 96 visit must be available and reviewed for participants who choose to transition direct to injection. Participants with ongoing safety issues or laboratory abnormalities of clinical concern (e.g., Grade 3 or Grade 4 liver enzyme elevations), will require consultation and agreement with the Medical Monitor prior to proceeding directly to injections in the Extension Phase.

If a clinical chemistry retest is required based on Week 96 labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 96). Participants will remain on oral ABC/DTG/3TC until the Week 100 injection visit, and until any required Week 96 retest results are available for review.

At Week 100, eligible participants will take the last dose of ABC/DTG/3TC (or DTG + 2 NRTIs), and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg)

as initial loading doses. Clinical chemistries will also be assessed at Week 100. At Week 101, participants will return to the clinic for PK and safety assessments including clinical chemistries. The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104a and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104a, but not later than Week 104a, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (<u>but not preferred</u>). Following the Week 108 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 Receiving Optional Oral Lead-In in the Extension Phase

At Week 100, eligible participants who after discussion with the investigator, choose to receive the optional oral lead-in will initiate a 4 week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily. **It is not necessary to dose ABC/DTG/3TC on the day the participant begins the oral lead-in with CAB + RPV. However, if the participant takes ABC/DTG/3TC prior to coming into the clinic, initiation of oral CAB and RPV should continue as planned.** Clinical chemistries will also be assessed at Week 100. At Week 104a, following the 4 week CAB + RPV oral lead-in, participants will have additional safety assessments including clinical chemistries. In addition, central lab results and safety parameters from the Week 104a visit must be available and reviewed. If a clinical chemistry retest is required based on Week 104a labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 104a). Participants will remain on oral CAB 30 mg + RPV 25 mg until the Week 104b injection visit, and until any required Visit 104a retest results are available for review. **An HIV-1 RNA sample will not be collected at Week 104a for participants receiving the optional oral lead in, but will be obtained at the Week 104b visit to serve as the injection baseline viral load.**

Section 1.0 Protocol Synopsis for 201584, Analysis:

Rationale for change: to describe new Week 124 analysis.

New Text:

In descriptive analyses, antiviral response will be assessed according to the proportion of participants with and without oral lead-in who have HIV-1 RNA ≥50 c/mL at Week 124 (i.e., 24 weeks from initiation of CAB LA + RPV LA at Week 100, ±6 week analysis window, using the FDA Snapshot algorithm), with corresponding 95% confidence interval. No formal statistical comparison with respect to safety and efficacy outcomes will be performed.

Section 2.1. Study Rationale:

Rationale for change: to include information on the reason for assessing no oral lead-in.

Original Text:

Additionally, participants initially randomized to continue ABC/DTG/3TC will have an option to switch to CAB LA + RPV LA after completion of the Week 100 visit. Eligible participants (HIV-1 RNA <50 c/mL at Week 96) would transition to LA dosing, beginning ~~with 4 weeks oral CAB + RPV therapy at Week 100, and receiving the first IM CAB LA + RPV LA injections at Week 104b~~.

Revised Text:

Additionally, participants initially randomized to continue ABC/DTG/3TC will have an option to switch to CAB LA + RPV LA **at, or after,** completion of the Week 100 visit. **Amendment 04 of the FLAIR study will provide an opportunity to access an *optional* (vs mandatory) oral lead-in for these participants who transition to LA treatment at Week 100.** Eligible participants (HIV-1 RNA <50 c/mL at Week 96) would transition to LA dosing, beginning **at either Week 100 (direct to injection) or Week 104b (optional oral lead-in with CAB 30 mg and RPV 25 mg).**

Importantly, the oral lead-in during the early development program for CAB LA and RPV LA was instituted to minimize the risk of severe adverse drug reactions during LA dosing (e.g. acute hypersensitivity). The 4 week oral lead-in allowed for an evaluation of any untoward adverse events and an assessment of safety labs prior to initiation of LA therapy. To date, the principal safety risk identified with cabotegravir, following 3145 exposures to drug (oral and/or LA), is suspected DILI, which has occurred in a few individuals, all of whom were receiving oral CAB. The time to onset ranged between 4 weeks and one year and manifested as asymptomatic elevations of ALT, without compromise to hepatic function. Each participant fully recovered, with removal of investigational product, without hospitalization or intervention. During the Phase 3 ATLAS and FLAIR studies, no cases of DILI have been identified, during the oral lead-in period, or following initiation of LA dosing. There has been no evidence to date of a risk for clinically significant hepatotoxicity observed with cabotegravir. Additionally, throughout the development program to date, no cases of severe drug hypersensitivity or severe drug allergy have been observed. While the risk of idiosyncratic severe drug reactions cannot be fully excluded, the risk of occurrence is felt to be low, on the basis of safety data generated to date.

Based on blinded, instream review of ongoing Phase 3 aggregate AE data (from FLAIR, and ATLAS) and of individual case reports (SAEs), no new, emerging, drug related safety issues have been identified within the four week oral lead-in dosing period (e.g., hypersensitivity, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS], severe drug induced liver injury [DILI]) that would have precluded participants from proceeding to CAB LA + RPV LA injections during the Maintenance Phase of the studies. Additionally, review of accumulating data has

not identified any new safety issues occurring on CAB LA + RPV LA that were otherwise predictable based on oral exposure experience.

As a result of the accumulated safety data, which has been generated over the course of the Phase 1, 2 and 3 clinical studies, this amendment has been developed to generate safety, efficacy and PK data for the transition from oral ART to CAB LA + RPV LA without receiving an oral lead-in. These data are intended to inform regulatory discussions around the safe and effective direct to inject dosing option with CAB LA + RPV LA. The decision to dose with or without an oral-lead-in will be optional in this study, as elected by the study participant following informed consent discussions with the investigator.

At Week 124, a descriptive analysis will be conducted to assess antiviral response (HIV-1 RNA ≥50 c/mL) for participants who choose no oral lead-in. No formal statistical comparison will be performed with respect to safety and efficacy outcomes at Week 124.

Data from this optional oral lead in will provide valuable knowledge/insight into the evolution of the 'direct to injection' concept.

Section 4.1 Overall Design:

Rationale for change: to highlight direct to injection as an option for participants transitioning from ABC/DTG/3TC to CAB LA + RPV LA in the Extension Phase.

Original Text:

Participants randomized to ABC/DTG/3TC during the Maintenance Phase will continue ABC/DTG/3TC for at least an additional 100 weeks. Participants who successfully complete Week 100 (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.

Revised Text:

Participants randomized to ABC/DTG/3TC during the Maintenance Phase will continue ABC/DTG/3TC for at least an additional 100 weeks. Participants who successfully complete Week 100 (without meeting study defined withdrawal criteria and who remain virologically suppressed **through Week 96**: 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. **The transition from ABC/DTG/3TC to CAB LA + RPV LA within the Extension Phase can be completed with or without an oral lead-in prior to commencement of injectable treatment. The oral lead-in decision will be made by the participant in consultation with the investigator and must be appropriately documented.**

Section 4.2.5. Extension Phase:

Rationale for change: Text moved from the end of Section 4.2.5.2 to under main Section 4.2.5. heading as applicable to all participants who go into the Extension Phase:

Rearranged Text within section (deleted from the end of Section 4.2.5.2.):

All eligible participants who transition into the Extension Phase 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.

Participants not eligible to enter the Extension Phase will end their study participation (Week 100 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.

Section 4.2.5.1. Participants Entering from the CAB LA + RPV LA Arm

Rationale for change: Simplified text as this information is duplicate text provided in multiple sections, including Section 4.2.5.

Original Text:

All participants who successfully complete 100 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 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 4.2.5.2. Protocol Synopsis for 201584, Treatment Arms and Duration, Extension Phase (edited pieces included below – not inclusive of entire section):

Rationale for change: to highlight direct to injection as an option for participants transitioning from ABC/DTG/3TC to CAB LA + RPV LA in the Extension Phase.

Original Text:

Participants randomized to continue ABC/DTG/3TC 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 100 (no withdrawal visit needed).

~~Participants receiving ABC/DTG/3TC with a Week 96 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 100. Clinical chemistries will be assessed ~~at Week 100~~. At Week 104a, 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 104a visit must be available and

reviewed before the Week 104b visit. If a clinical chemistry retest is required based on Week 104a labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 104a). Participants will remain on oral CAB 30 mg + RPV 25 mg until the Week 104b injection visit, and until any required Visit 104a retest results are available for review.

Revised Text:

Participants randomized to continue ABC/DTG/3TC 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 100 (no withdrawal visit needed). **The transition from ABC/DTG/3TC to CAB LA + RPV LA within the Extension Phase can be completed with or without an oral lead-in prior to commencement of injectable treatment. The participant's decision will be taken in consultation with the investigator and must be appropriately documented. As participants approach the Week 100 visit, sites must ensure sufficient CAB and RPV supply are available to support the participant's decision for transition to LA.**

Participants Transitioning Direct to Injection in the Extension Phase:

Central lab results and safety parameters from the Week 96 visit must be available and reviewed for participants who choose to transition directly to injections. Participants with ongoing safety issues or laboratory abnormalities of clinical concern (e.g. Grade 3 or Grade 4 liver chemistry elevations) will require consultation and agreement with the Medical Monitor prior to proceeding directly to injections in the Extension Phase.

If a clinical chemistry retest is required based on Week 96 labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 96). Participants will remain on oral ABC/DTG/3TC until the Week 100 injection visit, and until any required Week 96 retest results are available for review.

At Week 100, eligible participants will take the last dose of ABC/DTG/3TC (or DTG + 2 NRTIs), and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg) as initial loading doses. Clinical chemistries will also be assessed at Week 100. At Week 101, participants will return to the clinic for PK and safety assessments including clinical chemistries. The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104a and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104a, but not later than Week 104a, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (<u>but not preferred</u>). Following the Week 108 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 Receiving Optional Oral Lead-In in the Extension Phase:

As participants approach the Week 100 visit, sites must ensure sufficient oral CAB and RPV are available for participants who choose to use the oral lead-in.

At Week 100, eligible participants who after discussion with the investigator, choose to receive the optional oral lead-in will initiate a 4 week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily**. It is not necessary to dose ABC/DTG/3TC on the day the participant begins the oral lead-in with CAB + RPV. However, if the participant takes ABC/DTG/3TC prior to coming into the clinic, initiation of oral CAB and RPV should continue as planned.**

Section 4.5.1. Dose Justification, Oral Lead-In Phase:

Rationale for change: to discuss ART coverage for participants who choose no oral CAB + RPV lead-in when transitioning from ABC/DTG/3TC to LA.

New Text Added:

The oral lead-in for participants randomized to the ABC/DTG/3TC arm who choose to receive CAB LA + RPV LA during the Extension Phase of the study is optional. Without oral lead-in dosing, CAB LA and RPV LA achieve concentrations following their initial injections similar to induction doses of their respective efficacious oral products. Oral ABC/DTG/3TC administered up to and including the day of the initial CAB LA + RPV LA injections will provide additional exposure to active antiviral agents during the transition from oral to LA treatment (e.g., exposure that would replace oral CAB + RPV exposure).

Section 4.6.1. Risk Assessment Oral CAB and CAB LA (GSK1265744/ GSK1265744 LA):

Rationale for change: to update information relating to no oral lead-in.

Original Text:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug Induced Liver Injury	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 ALT elevation). In some of these participants' transient transaminitis were explained by acute hepatitis C infection and whilst a small number of others did not have alternative explanations, suggesting a mild form of 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 LA or Placebo LA 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 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 period ~~is being~~ implemented ~~in~~ this study, where all participants will receive oral CAB prior to the administration of CAB LA 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 7.4.5.1 of this protocol. Participants will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		withdrawn from CAB treatment where no compelling alternative cause is identified and DILI is suspected • Participants who develop ALT ≥3 times ULN while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA. • All instances of liver transaminase elevations of Grade 2 and above will be followed to resolution. Participants withdrawn from CAB treatment due to meeting liver chemistry stopping criteria will be regularly monitored ~~and~~ both clinically and using liver chemistries to determine progress towards resolution of the liver event.
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 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.	• 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 will be given 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,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	None of the ISRs reported to date was serious and no clinically significant complications were reported.	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. • Specialist dermatology consultation will be sought if warranted for individual participants.
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 CAB LA. The long exposures anticipated after CAB LA injection may complicate the management of a drug hypersensitivity reaction, were it to occur.	• The risk of developing a hypersensitivity reaction post administration of CAB LA ~~will be~~ minimized by the use of a 4-week oral lead-in of CAB to determine individual safety and tolerability prior to the introduction of CAB LA. • Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study (refer to Time & Events Table). Results from these assessments may aid early detection of HSR. • Oral CAB will be withdrawn immediately for cases with suspected HSR during the oral lead-in phase. During oral and CAB LA treatment, any HSR reactions that occur would be managed supportively

Revised Text:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug Induced Liver Injury	A small proportion of participants in the CAB program to date (total exposure **>3100 participants**) have developed transaminitis (elevated liver transaminases characterised by predominant ALT elevation). In some of these participants' transient transaminitis were explained by acute hepatitis C infection and whilst a small number of others did not have alternative explanations, suggesting a mild form of DILI without hepatic dysfunction which resolved upon withdrawal of treatment with CAB. Of the **four** participants with possible or probable cases of DILI identified in Phase 2 studies, all were receiving oral CAB.	• Exclusion criteria as described in Section 5.2 will prohibit participants with significant liver impairment based on screening liver chemistry including transaminases (ALT and 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 period **was** implemented **at the beginning of** this study, where all participants will receive oral CAB prior to the administration of CAB LA to determine individual safety and tolerability. **During the Extension Phase of the study, following review of available oral lead-in and Maintenance Phase safety data, the protocol was amended to allow an optional oral lead-in for the participants transitioning from ABC/DTG/3TC to CAB LA+RPV LA.** • 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 7.4.5.1 of this protocol. Participants will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		withdrawn from CAB treatment where no compelling alternative cause is identified and DILI is suspected. • Participants who develop ALT ≥3 times ULN while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA. • All instances of liver transaminase elevations of Grade 2 and above will be followed to resolution. Participants withdrawn from CAB treatment due to meeting liver chemistry stopping criteria will be regularly monitored both clinically and using liver chemistries to determine progress towards resolution of the liver event.
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 receiving multiple injections. Although some Grade 3 ISRs were reported, **the majority of** ISRs have not**,** to date**,** been associated with an excess of participants' withdrawal. None of the ISRs reported to date was serious and	• 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 will be given 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,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	no clinically significant complications were reported.	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. • Specialist dermatology consultation will be sought if warranted for individual participants.
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 CAB LA. The long exposures anticipated after CAB LA injection may complicate the management of a drug hypersensitivity reaction, were it to occur.	• The risk of developing a hypersensitivity reaction post administration of CAB LA **was** minimized **at the start of the study** by the use of a **mandatory** 4-week oral lead-in of CAB to determine individual safety and tolerability prior to the introduction of CAB LA. **During the Extension Phase of the study, following review of available oral lead-in and Maintenance Phase safety data, the protocol was amended to allow an optional oral lead-in for the participants transitioning from ABC/DTG/3TC to CAB LA+RPV LA.** • Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study (refer to Time & Events Table). Results from these assessments may aid early detection of HSR.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Oral CAB will be withdrawn immediately for cases with suspected HSR during the oral lead-in phase. During oral and CAB LA treatment, any HSR reactions that occur would be managed supportively

Section 4.6.1. Risk Assessment Oral RPV and RPV LA:

Rationale for change: to update information relating to no oral lead-in.

Original Text:

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'	• 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	withdrawal due to ISRs. ~~None of the ISRs was serious and no clinical significant complications were reported.~~	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. • Specialist dermatology consultation will be sought if warranted for individual participants.
Rash	Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are Grade 1 or Grade 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	• ~~In~~ this study, RPV LA administration ~~will be~~ preceded by a four week 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. • Participants experiencing a grade 3 or 4 rash should discontinue their ART medication and will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	serum biochemistries.	withdrawn from the study. • All rash events should be assessed 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.

Revised Text:

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	• 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, **the majority of ISRs** have not, to date, been associated with an excess of participants' withdrawal due to ISRs.	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. • Specialist dermatology consultation will be sought if warranted for individual participants.
Rash	Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are Grade 1 or Grade 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	• **At the beginning of** this study, RPV LA administration **was** preceded by a four week oral RPV lead-in to evaluate safety and tolerability in individual participants. **During the Extension Phase of the study, following review of available oral lead-in and Maintenance Phase safety data, the protocol was amended to allow an optional oral**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	**lead-in for the participants transitioning from ABC/DTG/3TC to CAB LA+RPV LA.** • 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. • Participants experiencing a grade 3 or 4 rash should discontinue their ART medication and will be withdrawn from the study. • All rash events should be assessed 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.

Section 5. Selection of Study Population and Withdrawal Criteria

Rationale for change: Similar text duplicated in Section 5.1. and Section 5.2.

Text Deleted:

~~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.~~

Section 6.3. Dose and Administration

Rationale for change: Table revised to explain direct to inject dosing option during the Extension Phase.

Original Text:

Extension Phase (Week 100 through End of Study)	
CAB LA + RPV LA Arm – continue IM dosing Every 4 Weeks+	
ABC/DTG/3TC Arm (Transition to CAB LA + RPV LA)*	
Oral Lead-In	
Week 100 to Week 104a (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 Injection (Loading Dose) – Week104b^	
Week 104b^ (two 3 mL injections once)	Receive <u>last dose</u> of <u>oral</u> CAB + RPV Receive CAB LA 600 mg given as 1 X <u>3 mL</u> IM injection Receive RPV LA 900 mg given as 1 X <u>3 mL</u> IM injection

Maintenance Injections – Every 4 Weeks following Week 104b	
Week 108 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

Revised Text:

Extension Phase (Week 100 through End of Study)	
CAB LA + RPV LA Arm – continue IM dosing Every 4 Weeks+	
ABC/DTG/3TC Arm (Transition to CAB LA + RPV LA)* - Optional Oral Lead-In	
Dosing If Using Optional Oral Lead-In	
Week 100 to Week 104b (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 Injection (Loading Dose) – Week104b^ **- Optional Oral Lead-In**	
Week 104b^ (two 3 mL injections once)	Receive last dose of oral CAB + RPV 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 following Week 104b **– Optional Oral Lead-In**	
Week 108 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
ABC/DTG/3TC Arm (Transition to CAB LA + RPV LA)*	
Direct to Inject Dosing - if *Not Using* Oral Lead-In	
First Injection (Loading Dose) – Week100^ - No Oral Lead-In	
Week 100^ (two 3 mL injections once)	**Receive last dose of oral ABC/DTG/3TC 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 <u>following</u> Week 100 – No Oral Lead-In	
Week 104a forward **(two 2 mL injections every 4 weeks)**	**Receive CAB LA 400 mg given as 1 X <u>2 mL</u> IM injection** **Receive RPV LA 600 mg given as 1 X <u>2 mL</u> IM injection**

Section 6.9.1. IM Dosing

Rationale for change: Text moved to before Extension Phase dosing transition for participants beginning LA dosing in the Extension Phase

Rearranged text within Section 6.9.1. and addition of Week 101 to one week post dose visits**:**

At one-week post dose visits (Week 5, Week 41, **and Week 101**), 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.**

Section 6.9.1. IM Dosing

Rationale for change: To explain dosing transition into the Extension Phase using optional oral lead-in.

Original Text:

~~Participants who were randomized to the ABC/DTG/3TC arm and are 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 100.~~

New Text Added:

Transition from ABC/DTG/3TC to IM Dosing into the Extension Phase:

Participants who were randomized to ABC/DTG/3TC and are eligible to enter the Extension Phase will transition to IM dosing at, or after, Week 100. The transition from ABC/DTG/3TC to CAB LA + RPV LA can be completed with or without an oral lead-in prior to commencement of injectable treatment. The participant decision will be taken in consultation with the investigator and appropriately documented. In order to ensure no interruption in study treatment, the transition into Extension should be performed as follows:

Participants Transitioning Directly to Injections in the Extension Phase:

Central lab results and safety parameters from the Week 96 visit must be available and reviewed for participants who choose to transition direct to injection. If a clinical chemistry retest is required based on Week 96 labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Week 96). Participants will remain on oral ABC/DTG/3TC until the Week 100 injection visit, and until any required Week 96 retest results are available for review.

At Week 100, eligible participants will take the last dose of ABC/DTG/3TC (or DTG + 2 NRTIs), and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg) as initial loading doses. Clinical chemistries will also be assessed at Week 100. At Week 101, participants will return to the clinic for PK and safety assessments including clinical chemistries. The second and third injections (CAB LA 400 mg + RPV LA 600 mg) will be administered at Week 104a and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104a, but not later than Week 104a, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (<u>but not preferred</u>). Following the Week 108 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 Receiving Optional Oral Lead-In in the Extension Phase:

At Week 100, eligible participants who after discussion with the investigator, choose to receive the optional oral lead-in will begin a 4 week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily. It is not necessary to dose ABC/DTG/3TC on the day the participant begins the oral lead-in with CAB + RPV. However, if the participant takes ABC/DTG/3TC prior to coming into the clinic, initiation of oral CAB and RPV should continue as planned.

Section 7.1. Time and Events Table:

Rationale for change: Updated to reflect changes for transition into the Extension Phase based on Oral Lead-In Design.

Original Text:

Participants originally randomized to ABC/DTG/3TC at Day 1, who choose to continue into the Extension Phase and transition to CAB LA + RPV LA, will have all assessments noted in the Time and Events table below performed Q4W ~~from Week 108~~ through Week 124.

Revised Text:

Participants originally randomized to ABC/DTG/3TC at Day 1, who choose to continue into the Extension Phase and transition to CAB LA + RPV LA, will have all assessments noted in the Time and Events table below performed Q4W through Week 124.

Section 7.1. Time and Events Table:

Rationale for change: Updated to reflect changes for transition into the Extension Phase based on Oral Lead-In Design.

Changes made to Table: New columns added to describe assessments for Direct to Inject Arm (changes to table noted in teal)

Procedures	Maintenance Phase by Week	Extension Phase by Week				
	100	101 – Direct to Inject Arm	104a – Direct to Inject Arm	104a LA and Oral Lead-In Arm	104b – Oral Lead-In ~~Switch~~ Arm	108
Symptom Directed Physical Exam and Medical Assessment [d]	X	X	X	X	X	X
HIV Associated Conditions	X	X	X	X	X	X
AE and SAE Assessment, Con Meds	X	X	X	X	X	X
ISR Assessment (LA Arm Only)	X	X	X	X	X	X
Clinical Chemistry	X		X	X		X
Pregnancy Testing[j]	U[j]S		S	S	U	S
HIV-1 RNA and sample for storage[k]	S[k]		X		X	X
PK Sample	X	X[v]	X[v]		X[v w]	S
IM Study Treatment Administration – Q4W throughout Maintenance and Extension Phase	X		X	X	X[s]	X

Also clarified Oral Lead-In Dispensing and Accountability for participants using optional oral lead-in only.

Procedures	Week 100	Week 104a	Week 104b
Oral CAB and Oral RPV Dispensation	X[x] **OLI Only**	X[x] **OLI Only**	
ABC/DTG/3TC Dispensation (or DTG alternate)			
Study Treatment Accountability (pill counts)	X **OLI Only**	X **OLI Only**	**X[u]** **OLI Only**

Table Footer and Footnotes Amended (only edited footnotes included below):

Note: Footnote i clarifies differences in eCSSRs for participants receiving ABC/DTG/3TC after Week 48 (based on every 8 week visits compared to continued Q4W visits for participants on LA).

Follow Up Visit: Conduct ~4 weeks after the last dose of oral IP. Required only if the participant has ongoing AEs / lab abnormalities at the last on-study visit. This visit may be conducted by telephone.
Direct to Inject: Participants transitioning into the Extension Phase who do *not* use the optional CAB + RPV oral lead-in beginning at Week 100.
Oral Lead-In: Participants transitioning into the Extension Phase who do use the optional CAB + RPV oral lead-in beginning at Week 100.
LA Arm: Participants who were originally randomized to CAB LA + RPV LA at Day 1.
Switch Arm: All participants who transition into the Extension Phase from ABC/DTG/3TC (or DTG + 2 NRTI's) at Week 100 – e.g., both direct to inject and oral lead-in participants.

i. On Day 1, the eC-SSRS is to be administered prior to randomization. During the Maintenance Phase, the eC-SSRS will be administered at each Q4W visit through the Week 48 primary endpoint, and then followed by Q12W **assessments for CAB LA + RPV LA arm**, thereafter through Week 96 **(LA:** Week 60, 72, 84, 96). **The ABC/DTG/3TC arm will have assessments at Week 72 and Week 96**. Preferably completed at the beginning of the visit following administration of other patient reported questionnaires required prior to injections

v. Take PK samples pre-dose. **At** Week 4b (and Week 104b for participants transitioning to LA from ABC/DTG/3TC **using the optional oral lead-in), the pre-dose** PK sample should be taken after review of the PK diary and prior to the final oral CAB + RPV dose. A sample will be **also be** taken at Week 4b, Week 48, and Week 96 (**and Week 100 [direct to inject] or** Week 104b **[using CAB + RPV oral lead-in]**), approximately 2 hours post-injections. The Week 5, Week 41, **and Week 101** visit can be performed at any time from 3 to 10 days after the Week 4b, Week 40, **and Week 100**

injection, respectively. PK samples at Week 5, Week 41, **and Week 101** can be taken at any time during the visit.

w. Participants should take the last dose of oral CAB+RPV at Week 4b (and Week 104b for participants transitioning to LA from ABC/DTG/3TC **if using the optional oral lead-in**) in the clinic after PK sampling. **Participants should take the last dose of ABC/DTG/3TC at Week 100 if transitioning directly to injections at Week 100. I**njections should be administered within 2 hours **of the last oral dose** where possible.

Section 7.4.3.1. Adverse Events and Serious Adverse Events (SAEs)

Rationale for change: Bullet removed as all AEs will be collected during Extension and Long-Term Follow-Up Phase (not just AEs leading to Withdrawal):

Deleted Text:

- ~~During the Extension Phase and Long-Term Follow-Up Phase, AEs leading to Withdrawal and all SAEs will be recorded~~.

Section 7.4.3.4. Prompt Reporting of Serious Adverse Events and Other Events

Rationale for change: clarification that ABC HSR will be collected for participants receiving ABC in the Long-Term Follow-Up Phase.

Original Text:

Suspected ABC HSR in participants randomized to the STR arm	1 week	ABC HSR eCRF	1 week	Updated ABC HSR eCRF

Revised Text:

Suspected ABC HSR in participants randomized to the STR arm **or receiving an oral ABC-containing regimen during the Long-Term Follow-Up Phase**[a]	1 week	ABC HSR eCRF	1 week	Updated ABC HSR eCRF

Section 7.4.7.1. Pregnancy Testing

Rationale for change: Clarification added for negative pregnancy test at Week 100 if particpants choose no oral CAB + RPV lead-in.

Original Text:

Women of childbearing potential must have a negative pregnancy test at Screening, Baseline (Week [-20]), the first Induction Phase visit (Day 1), and Week 104b for women transitioning into the Extension Phase from the ABC/DTG/3TC arm (prior to administration of first CAB LA and / or RPV LA injections).

Revised Text:

Women of childbearing potential must have a negative pregnancy test at Screening, Baseline (Week [-20]), the first Induction Phase visit (Day 1), and **Week 100 (if no oral lead-in is used)** or Week 104b **(if using CAB and RPV oral lead-in)** for women transitioning into the Extension Phase from the ABC/DTG/3TC arm (prior to administration of first CAB LA and / or RPV LA injections).

Section 7.5.1. PK Sample Collection

Rationale for change: Clarification of text for optional oral lead-in.

Original Text:

At Week 4b (and Week 104b for participants transitioning into the Extension Phase from the ABC/DTG/3TC arm), PK samples must be collected within the window of 20 to 28 hours after the oral dose of CAB + RPV was taken the day prior to the clinic visit.

Revised Text:

At Week 4b (and Week 104b for participants **using the oral CAB + RPV lead-in and** transitioning into the Extension Phase from the ABC/DTG/3TC arm), PK samples must be collected within the window of 20 to 28 hours after the oral dose of CAB + RPV was taken the day prior to the clinic visit.

Section 7.5.1. PK Sample Collection

Rationale for change: Updated sampling schedule based on optional oral CAB + RPV lead-in during the Extension Phase.

Original Text (Table 8):

ABC/DTG/3TC Arm Transitioning to CAB LA + RPV LA at Week 100	CAB	Pre-Dose: Week 104b, Week 108, Withdrawal 2 Hours Post Dose: Week 104b Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
	RPV	Pre-Dose: Week 104b, Week 108, Withdrawal 2 Hours Post Dose: Week 104b 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± 7 days (4th and all subsequent injections); Sample Collection: Pre-dose at Week 4b (and Week 104b for participants transitioning from ABC/DTG/3TC 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.

a. Each analyte in individual collection tube.
b. Samples taken at Week 5, Week 41, may be collected from 3 to 10 days after Week 4b, Week 40, respectively. These samples may be collected at anytime during those visits.

Revised Text:

ABC/DTG/3TC Arm Transitioning to CAB LA + RPV LA at Week 100 **(participants using CAB + RPV oral lead-in)**	CAB	Pre-Dose: Week 104b, Week 108 **(for storage)**, Withdrawal 2 Hours Post Dose: Week 104b Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
	RPV	Pre-Dose: Week 104b, Week 108 **(for storage)**, Withdrawal 2 Hours Post Dose: Week 104b Long-term follow-up Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
ABC/DTG/3TC Arm Transitioning to CAB LA + RPV LA at Week 100 (Direct to Inject - participants *not* using CAB + RPV oral lead-in)	**CAB**	**Pre-Dose: Week 104a, Week 108 (for storage), Withdrawal** **2 Hours Post Dose: Week 100** **1 Week Post Dose[b]: Week 101** **Long-term follow-up Period (off-drug; storage sample)** **Months 1, 3, 6, 9, and 12**
	RPV	**Pre-Dose: Week 104a, Week 108 (for storage), Withdrawal** **2 Hours Post Dose: Week 100** **1 Week Post Dose[b]: Week 101** **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± 7 days (4th and all subsequent injections); Sample Collection: Pre-dose at Week 4b (and Week 104b for participants transitioning from ABC/DTG/3TC Arm **using oral lead-in**): 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.

a. Each analyte in individual collection tube.
b. Samples taken at Week 5, Week 41, **and Week 101** may be collected from 3 to 10 days after Week 4b, Week 40, **and Week 100**, respectively. These samples may be collected at anytime during those visits.

Section 9.2.4. Sample Size Considerations for Week 124 Extension Switch Analysis – New Section

Rationale for change: Text added regarding sample size for endpoint for Extension Phase endpoint.

New Text Added:

For the Week 124 Extension Switch population analysis (Section 9.3.1.6), the primary efficacy endpoint of interest is the proportion of participants without oral lead-in who have HIV-1 RNA ≥50 c/mL at Week 124 (i.e., 24 weeks from initiation of CAB LA + RPV LA, ±6-week analysis window, using the FDA Snapshot algorithm). The endpoint will be evaluated descriptively, with no formal statistical comparison to data generated in participants receiving oral lead-in by to initiation of CAB LA + RPV LA.

Table 14 presents the precision in estimation according to sample size and observed proportion with HIV-1 RNA ≥ 50 c/mL. For example, if the observed rate is 3% and 250 Extension switch participants do not receive oral lead-in, then the upper bound of the 95% CI would be 5.1%.

Table 14 Precision (Upper Limit of 95% CI) for Single Arm Proportion

Sample Size without Oral Lead-In	Observed Proportion HIV-1 RNA ≥ 50 c/mL	Upper limit of 95% Confidence Interval†
175	2%	4.1%
200	2%	3.9%
225	2%	3.8%
250	2%	3.7%
175	3%	5.5%
200	3%	5.4%
225	3%	5.2%
250	**3%**	**5.1%**
175	4%	6.9%
200	4%	6.7%
225	4%	6.6%
250	4%	6.4%

† Two-sided confidence Interval calculated using the Wald normal approximation method

Section 9.3.1.6. Extension Switch Population (ES) – New Section

Rationale for change: Explanation of population for participants switching from ABC/DTG/3TC to CAB LA + RPV LA in the Extension Phase.

New Text Added:

The Extension Switch population will include all participants randomized to the Maintenance Phase ABC/DTC/3TC arm who switch to and receive at least one dose of CAB and/or RPV during the Extension Phase of the study. The ES population will be used to evaluate safety and efficacy of switching to CAB LA + RPV LA, with

and without oral lead-in. Participants will be assessed according to actual treatment received during the Extension Phase.

Section 9.3.3. Planned Analyses

Rationale for change: To describe new Week 124 analysis for participants switching to LA during the Extension Phase.

Original Text:

At least ~~two~~ analyses will be conducted to evaluate ~~primary and secondary~~ objectives of the protocol, ~~one~~ after all subjects have completed their visit at Week 48 and one after Week 96.

Revised Text:

At least **three** analyses will be conducted to evaluate **the** objectives of the protocol: after **all randomized participants** have completed their visits at Week 48 and Week 96, **respectively, and after all Extension switch participants (Section 9.3.1.6) have completed the Week 124 visit.**

Section 9.4.2. Secondary Analyses

Rationale for change: Clarification of planned analyses.

Original Text:

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

Revised Text:

Proportion of participants with plasma HIV-1 RNA <200 c/mL and <50 c/mL, **and HIV-1 RNA ≥200 c/mL and ≥50 c/mL**, respectively, over time will be summarized using the Snapshot algorithm.

Section 9.4.2.1. Week 124 Extension Switch Analysis (New Section Added)

Rational for change: To describe new Week 124 planned analysis.

New Text Added"

Section 9.4.2.1. Week 124 Extension Switch Analysis

For the Week 124 Extension Switch population analysis (Section 9.3.1.6), antiviral response will be assessed according to the proportion of participants with and without oral lead-in, respectively, who have HIV-1 RNA ≥50 c/mL at Week 124 (i.e., 24 weeks from initiation of CAB LA + RPV LA, ±6 week analysis window, using the FDA Snapshot algorithm), with corresponding 95% confidence interval. The

primary efficacy endpoint of interest for this analysis is the proportion of participants without oral lead-in who have HIV-1 RNA ≥50 c/mL at Week 124. No formal statistical comparison with respect to safety and efficacy outcomes will be performed.

Proportion of participants with plasma HIV-1 RNA <200 c/mL and <50 c/mL and confirmed virologic failure, respectively, over time will be summarized.

Absolute values and change from Extension Baseline CD4+ cell count will be summarized over time.

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**

Changes from Extension Baseline in laboratory (including fasting lipids) and vital signs data will be summarized. In addition, the number and percentage of participants with Extension emergent graded laboratory toxicities (based on DAIDS categories) will be summarized by treatment group.

Further details for secondary efficacy, safety and exploratory analyses will be included in the RAP.

Section 12.7 Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

Rationale for change: Text updated to be consistent with current template language.

Original Text:

~~**Section 12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (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.~~

~~1. Contraceptive subdermal implantntrauterine device or intrauterine system~~

~~2. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])~~

~~3. Injectable progestogen [Hatcher, 2011]~~

~~4. Contraceptive vaginal ring [Hatcher, 2011]~~

~~5. Percutaneous contraceptive patches [Hatcher, 2011]~~

~~6. Male partner sterilization 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.~~

~~These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.~~

Revised Text:

Section 12.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

a. Premenarchal

b. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish

to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Section 12.7.1. Contraception Guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 17.

Table 17 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Two highly effective methods of contraception should be utilized from 30 days prior to the first dose of study medication, throughout the study, and for at least 52 weeks after discontinuation of CAB LA and RPV LA .

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed as per the study Time and Events Table.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing will be performed and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor / approved by the sponsor and in accordance with instructions provided in its package insert.