Objectives and Endpoints:

Objectives	Endpoints
Primary	
To demonstrate the antiviral activity of CAB LA + RPV LA every 2 months in suppressed HIV-1 infected antiretroviral therapy ART-experienced participants	Proportion of participants with HIV-RNA ≥50 c/mL as per food and drug administration (FDA) Snapshot algorithm at Month 12
Secondary	
To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every 2 months and oral DTG +RPV once daily.	Proportion of participants with plasma HIV-1 RNA <50 c/mL (c/mL) at Month 12 using the FDA Snapshot algorithm Proportion of participants with protocol-defined confirmed virologic failure (CVF) over time Proportion of participants with HIV-RNA greater than or equal to 50 c/mL as per FDA Snapshot algorithm over time Absolute values and changes from Baseline in viral load and cluster of differentiation 4 (CD4+) cell counts over time
To demonstrate the safety and tolerability of CAB LA + RPV LA every 2 months and oral DTG +RPV once daily.	Incidence and severity of adverse events (AEs) and laboratory abnormalities over time Proportion of participants who discontinue treatment due to AEs over time Change from Baseline in laboratory parameters over time
To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, DTG + RPV
To characterize CAB and RPV concentrations and population pharmacokinetics and identify important determinants of variability	Plasma pharmacokinetic (PK) parameters for CAB LA and RPV LA (when evaluable, trough concentrations [C_{trough}])

Procedures Q2M	**Day 1** [a]	**Month**													**WD** [l, m]
		2 [o]	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**[b]	**22**[b]	**24**	**26**	
Weight, Height & body mass index (BMI)[e]	X	X	X		X		X		X		X		X		X
HIV Associated Conditions, AE and serious adverse event (SAE) Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead electrocardiogram (ECG) [f]	X						X								X
Clinical Chemistry and Hematology	X	X	X		X		X		X		X		X		X
Pregnancy Testing (U)rine or (S)erum [g]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
HIV-1 RNA and sample for storage [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+	X	X	X		X		X		X		X		X		X
Urinalysis	X														X

Objectives	Endpoints
once daily	using the FDA Snapshot algorithm Proportion of participants with protocol-defined confirmed virologic failure (CVF) over time Proportion of participants with HIV-RNA greater than or equal to 50 c/mL as per FDA Snapshot algorithm over time Absolute values and changes from Baseline in viral load and CD4+ cell counts over time
To demonstrate the safety and tolerability of CAB LA + RPV LA every 2 months and oral DTG + RPV once daily	Incidence and severity of AEs and laboratory abnormalities over time Proportion of participants who discontinue treatment due to AEs over time Change from Baseline in laboratory parameters over time
To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and DTG + RPV
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, trough concentrations [C_{trough}])
To assess participant reported health-related quality of life, injection tolerability/acceptability, and treatment satisfaction.	Change from Baseline (Day 1) in HIVDQoL at Months 6 and 12 (or Withdrawal) Change from baseline (Day 1) in total "treatment satisfaction" score, and individual item scores of the HIV Treatment Satisfaction Status Questionnaire (HIVTSQs) at Months 6 and 12 (or Withdrawal) Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire HIVTSQc at Month

Participants in POLAR who successfully complete Week 300 in the LATTE study (without meeting study defined withdrawal criteria) will be given the option to receive either CAB LA + RPV LA (administered Q2M) or oral DTG + RPV daily until study intervention is either locally approved and commercially available within the local sector (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 + RPV LA Q2M is terminated.

Any participant who receives at least one dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason will enter a 52-week LTFU Phase. Those participants must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA.

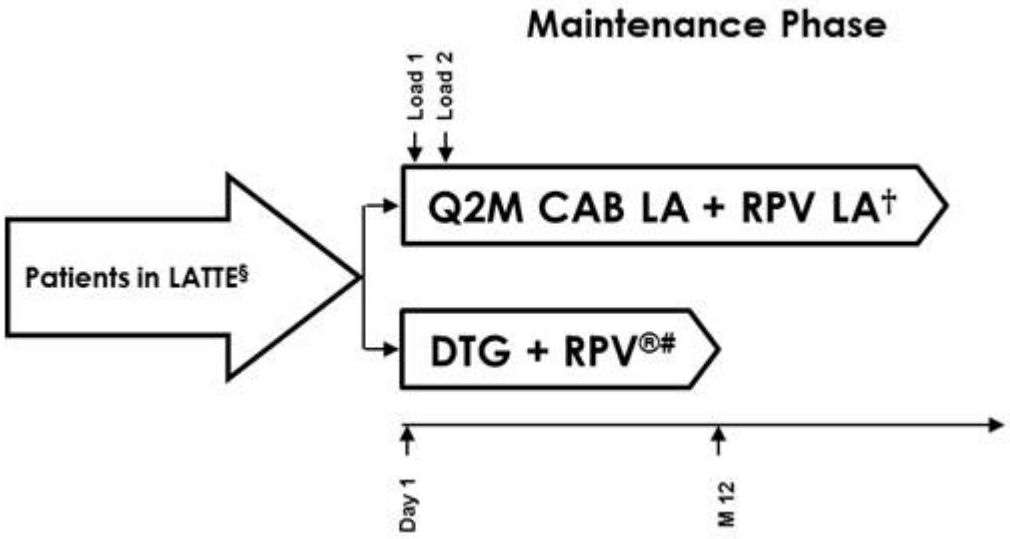
The primary endpoint for the study is the proportion of participants with HIV-RNA greater than or equal to 50 c/mL at Month 12 as per Food and Drug Administration (FDA) Snapshot algorithm using the Intent-to-Treat Exposed (ITT-E) population.

4.1.1. Evaluable Participants

The target population to be enrolled is HIV-1 infected virologically suppressed (HIV-1 RNA <50 c/mL) participants on stable ART who have completed, at minimum, Week 312 (or Week 324 in the event of unavoidable delays) of the LATTE study. It is anticipated that approximately 100 participants will be enrolled into POLAR (see Section 10.2).

4.1.2. Study Schematic

Figure 1 209035 (POLAR) Study Design Schematic



§ All participants in LATTE administered oral CAB 30 mg + RPV 25 mg
† Access commercially once Q8W is approved
# Access longer term via commercial route. Participants will continue to receive DTG + RPV if located in a region where not commercially available.

4.2. Treatment Groups and Duration

4.2.1. Eligibility for the POLAR Study for Participants Entering from the LATTE Study

Informed consent must be obtained prior to any study procedures, including any Day 1 assessment.

All participants with an undetectable HIV-1 RNA (<50 c/mL) at Week 300 in the LATTE study are eligible to enter this study. A single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor. Participants with HIV-1 RNA ≥200 c/mL at Week 300 are not eligible to enter the study and will not be allowed a repeat to determine eligibility. The Day 1 visit of the POLAR study will be performed in parallel with the final closeout visit for the LATTE study, Week 312 or (if contracts have not been finalized and/or institutional review board (IRB) approval has not been obtained by Week 312 in the LATTE study) Week 324.

Result of HIV-1 RNA at Week 300	Action
<50 c/mL	Begin POLAR study at Day 1
≥50 c/mL but <200 c/mL	Single repeat allowed only after consultation and approval from medical monitor
Single repeat <50 c/mL	Begin POLAR study at Day 1
Single repeat ≥50 c/mL	Cannot begin POLAR and must be withdrawn from the LATTE study; Complete withdrawal visit.
≥200 c/mL	Cannot begin POLAR and must be withdrawn from LATTE; Complete withdrawal visit.

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

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, study eligibility will be determined ONLY in consultation with the medical monitor.

Participants ineligible for this study will be withdrawn from LATTE.

4.2.2. Maintenance Phase (Day 1 up to Commercial Approval)

At the Day 1 visit (the start of the first month of the study), participants will return to the clinic, take the last dose of their oral (CAB 30 mg + RPV 25 mg), and receive the first

The 200056 (LATTE-2) (GlaxoSmithKline Document Number 2013N168152_05) clinical trial evaluated a different simplification approach and served as proof of concept for POLAR. In 200056, HIV-1 RNA suppression was induced with a three-drug antiretroviral regimen consisting of CAB + ABC/3TC FDC, and then participants switched to a two-drug two-class regimen consisting of CAB LA + RPV LA for the maintenance of HIV-1 RNA suppression. Results demonstrate that through 96 weeks on two-drug maintenance therapy, 94% (Q8W IM arm) and 87% (Q4W IM) of participants maintained virologic suppression (HIV-1 RNA <50 c/mL) compared to 84% of participants continuing oral CAB + 2 NRTIs. CAB LA + RPV LA was well tolerated through Week 96 for both the Q8W and Q4W dosing regimens, as demonstrated by a low discontinuation rate due to AEs, including injection site reaction (ISR) related AEs in either dosing arm, with no significant dose-dependent trends in safety parameters. On the basis of 200056 Week 48, and Week 96 data, Q4W and Q8W IM dosing are being progressed into Phase 3 for further clinical development, respectively. The CAB LA + RPV LA Q8W regimen is currently under evaluation in the ongoing Phase IIIb ATLAS-2M study.

Participants electing to receive CAB LA + RPV LA Q2M IM administration will be required to participate in clinic visits approximately every 2 months while participants electing to receive oral DTG + RPV administration will be required to participate in clinic visits approximately every 3 months. Importantly, secondary objectives of this study are to understand the acceptability, tolerability, and patient reported preferences to the novel injectable regimen. 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. If the Q2M arm were required to receive blinded placebo tablets every day, the value of comparing safety, tolerability, and convenience of Q2M compared to oral administrations would be limited and include overly burdensome visit requirements for those randomized to Q2M administration. Additionally, the perceived value for participants to transition from the LATTE study to POLAR to receive the Q2M regimen would also be limited and may result in loss of patients with prior oral 2 drug regimen experience, thereby limiting the ability to compare and evaluate the experience gained after 6 years of treatment on an oral 2 drug regimen plus Q2M regimen administration within individual participants.

Due to the complexities, lack of feasibility and limitations of blinding CAB LA and RPV LA injections for Q2M compared to oral DTG + RPV administration, this Phase 2b study is planned as open label.

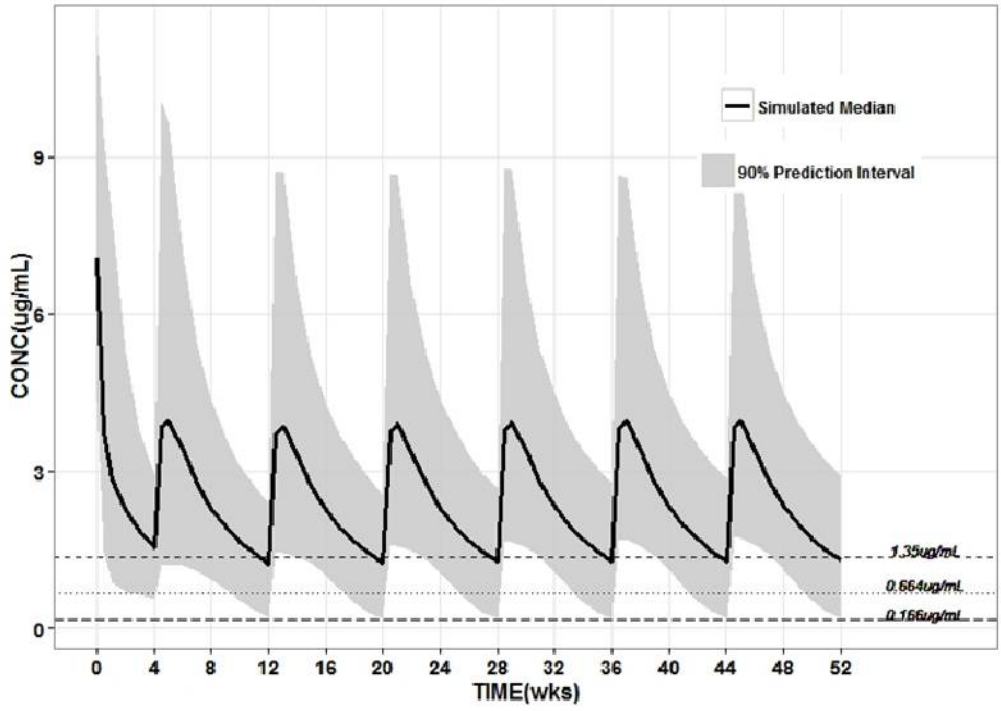
To maintain the integrity of the trial, data aggregated by actual treatment group will not be made available to members of the Study Team nor Investigators in advance of the primary analysis. Lastly, ascertainment bias affecting the primary efficacy analysis is unlikely since the primary endpoint is inherently objective, being primarily determined by HIV-1 RNA laboratory assessment. The open label design should therefore have no impact on the analysis of study endpoints.

LATTE-2, an additional Phase 3b study ATLAS 2M was initiated to further evaluate bimonthly (Q2M) dosing of CAB LA 600 mg IM and RPV LA 900 mg IM administered upon initiation of long-acting treatment and again one month after the initial injection then Q2M thereafter. POLAR will transition subjects in LATTE receiving oral CAB 30 mg and RPV 25 mg once daily to the Q2M regimen.

4.4.1.1. CAB LA Q2M

The CAB LA 600 mg Q2M regimen is predicted to achieve concentrations above 1.35 μg/mL, the geometric mean trough concentration (Cτ) following oral CAB 10 mg once daily, which was shown to be efficacious in the LATTE study. The lower bound of the 90% prediction interval is approximately 0.166 μg/mL, indicating that 95% of participants on this regimen should remain above the PA-IC_{90} throughout dosing (Figure 2). The CAB LA Q2M regimen consists of identical 600 mg doses administered at Day 1, Month 2, and Q2M thereafter. Observed data for the optimized Q2M regimen in LATTE-2 Extension Phase were consistent with predictions, with a geometric mean CAB trough concentration of 1.58 μg/mL 4 weeks following the reduced 600 mg IM loading dose and of 2.03 μg/mL following the fourth injection.

Figure 2 Simulated* Median (90% Prediction Interval [PI]) CAB Plasma Concentrations versus Time for the Optimized CAB LA Q8W Regimen (600 mg IM Day 1, Week 4, Q8W Thereafter)



*Note: current simulations based on interim plasma concentration dataset

A one-week delay in CAB LA dosing for the Q2M regimen at steady state is predicted to result in ~92% rather than 95% of participants achieving trough concentrations above the PA-IC90, which is considered acceptable.

8.1. Time and Events Table

8.1.1. Time and Events Table for CAB LA + RPV LA Q2M Administration

Procedures Q2M	Day 1 [a]	Month													WD [l, m]
		2 [o]	4	6	8	10	12	14	16	18	20[b]	22[b]	24	26	
Written Informed Consent	X														
Demography	X														
Eligibility Verification	X														
Physical Exam	X														
Medical History	X														
CDC Classification	X														
Rapid Plasma Reagin (RPR)	X														
Symptom Directed Physical Exam, ISR and Medical Assessment [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (blood pressure [BP], heart rate [HR]) [d]	X	X	X		X		X		X		X		X		X
Weight, Height & body mass index (BMI) [e]	X	X	X		X		X		X		X		X		X

Procedures Q2M	**Day 1** [a]	**Month**													**WD** [l, m]
		2 [o]	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**[b]	**22**[b]	**24**	**26**	
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [f]	X						X								X
Clinical Chemistry and Hematology	X	X	X		X		X		X		X		X		X
Pregnancy Testing (U)rine or (S)erum [g]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
HIV-1 RNA and sample for storage [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+	X	X	X		X		X		X		X		X		X
Urinalysis	X														X
Fasting Glucose, Cholesterol (Total, high density lipoprotein [HDL] and low density lipoprotein [LDL]) and Triglycerides [i]	X						X						X		X
Prothrombin time (PT)/ Partial Thromboplastin Time (PTT)/international normalized ratio (INR)	X														X

Procedures for DTG+RPV	Day 1 [a]	Month 3	Month 6	Month 9	Month 12	WD [j]	Notes
Plasma for Storage [f]	X	X	X	X	X	X	
PK Sample for Storage						S	
Clinical Chemistry and Hematology	X	X	X	X	X	X	
Pregnancy Testing [g]	U	U	U	U	U	U	
Urinalysis	X					X	
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [h]	X					X	
PT/PTT/INR	X					X	
HIVTSQc					X	X	
HIVTSQs	X		X		X	X	
HIVDQoL	X		X		X	X	
Participant Visit Reminder Contact	X	X	X	X	X		
Participant Contact Detail Confirmation	X	X	X	X	X		
Study intervention Dispensation [i]	X	X	X	X	X		

8.2. Baseline Assessments

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

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

Baseline information to be collected at Day 1 includes general medical history and current medical conditions. Laboratory and health outcomes assessments will also be assessed. Questionnaire/surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted, in the order specified. For participants who agree to the optional assessment, a whole blood sample for genetic research should be collected at Day 1 (if not already collected during participation in the LATTE study).

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

- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at Baseline and assessments will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. In addition, medical history/risk factors for renal disease such as nephropathy, renal failure, and nephrolithiasis will be assessed.

- history of illicit drug use [e.g., cocaine, heroin, and methamphetamine use]);

- intravenous drug use history;

- gastrointestinal disease (e.g., gastrointestinal [GI] bleeding, peptic ulcer disease [PUD], etc);

- metabolic (e.g., Type I or II diabetes mellitus);

- psychiatric (e.g., depression);

- renal (e.g., nephrolithiasis, nephropathy, renal failure); and,

- neurologic disorders

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

and has been performed in the timeframe of the study. Where possible local lab results should be confirmed by submission of samples to the central lab.

8.3. Efficacy Assessments

8.3.1. Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events schedule (Section 8.1). 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.

8.3.2. 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 8.1) and Laboratory Assessments (Section 8.4.2).

8.3.3. HIV Associated Conditions

HIV-associated conditions will be recorded as per Time and Events schedule (Section 8.1). HIV-associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection (see Section 12.8).

8.4. Safety Assessments

8.4.1. Clinical Evaluations

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

- Monitoring and recording of all AEs and SAEs. Additional information on the Time Period and Frequency of Detecting AEs and SAEs is provided in Section 8.5.2.
- Physical exams should be conducted as part of normal routine clinical care. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).
- Height and weight will be measured and recorded. Height collected on the Day 1 (Baseline) only.
- Vital signs will include systolic and diastolic blood pressure and heart rate collected after resting for about 5 minutes. Temperature will also be collected.
- Past medical history, family history, social history, medication history. Targeted history on cardiovascular risk (smoking history, family and personal history).
- HIV-associated conditions will be recorded.

- Electrocardiogram: A 12-lead ECG will be performed in a semi-supine position after 5 minutes of rest. On Day 1 (Baseline) of the Maintenance Phase, ECGs should be performed in triplicate prior to first dose. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each participant for the site. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations. The same QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- Regular monitoring of hematology, blood chemistry, and fasting glucose and lipids (parameters to be tested listed below).
- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of CAB LA or RPV LA or as required by the Medical Monitor following a treatment interruption(s). If serum testing is required locally, the results should be available prior to the visit where urine testing is indicated per the Time and Events Schedule (Section 8.1).
- Evaluation and documentation of all concomitant medications and blood products.
- Injection Site Reactions (ISRs) will be assessed clinically during the Maintenance and Extension Phases for the following:

  Pain, tenderness, pruritis, warmth, bruising, discoloration, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).
- A clinical assessment (using Division of Acquired Immunodeficiency Syndrome [DAIDS] grading scale) should be performed both before and after an injection to identify resolving and new ISRs. All injection site reactions are considered adverse events. The clinical assessment and interpretation of any ISR, will be documented in the ISR AE eCRF.

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

8.4.2. Laboratory Assessments

All protocol required laboratory assessments, as defined in the Time and Events Schedule (see Section 8.1), must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labeled with the participant number, protocol number, site/center 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.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in

the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, must be conducted in accordance with the laboratory manual and the protocol Time and Events table.

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 12.3 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events").

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

Table 3 includes lab parameters to be assessed as per the Time and Events Schedule (see Section 8.1). In addition to the protocol-specified laboratory assessments the study Medical Monitor, in collaboration with the site investigator, may request additional central laboratory assessments be performed to support safety profiling and case management of individual study participants.

Height and weight will also be measured and recorded as per the Time and Events Table in Section 8.1 above.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- The site of IM injection administration should be assessed at every visit for signs of any possible reaction. See Section 8.7.9 for additional information.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.4. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate. These will be recorded as per the Time and Events Table in Section 8.1.

8.4.5. Electrocardiograms

A 12-lead ECG will be performed in a semi-supine position. On Day 1, ECGs should be performed in triplicate prior to first dose. At Day 1, a 2 hour post dose ECG will be performed for all participants. ECG evaluations at other visits should be obtained after dosing, preferably 2-4 hours post dosing. The 2-hour post dose ECG on Day 1 can also be used for the LATTE Week 312 (or Week 324, if needed) visit. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each participant. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations. Refer to the Time and Events Table for collection timepoints (Section 8.1). Refer to Section 7.1.2 for [QTc] withdrawal criteria and additional [QTc] readings that may be necessary.

8.4.6. Suicidal Ideation and Behaviour 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 DTG. 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

- 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 12.4, Appendix 4.
- 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 intervention or study participation, the investigator must promptly notify GSK.

8.5.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4, Section 12.4

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?"

8.5.3. 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 8.7) 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 7). Further information on follow-up procedures is given in Section 12.4, Appendix 4).

8.5.4. 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 4 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 4.

Criteria for liver chemistry stopping and follow-up criteria are in Section 7.1.1.

Table 4 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 (CV) or death event	Initial and follow-up reports to be completed when the cardiovascular event or death is reporteda	"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 reporteda	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 hours	"Pregnancy Notification Form"	Within 24 hours of investigator awareness of pregnancy outcome	"Pregnancy Follow-up Form" and SAE if required
Seizure or suspected seizure	24 hours	eCRF	24 hours	eCRF
Suspected ABC HSR in participants receiving Oral standard of care (SOC) during the Long-Term Follow-Up Phaseb	1 week	ABC HSR eCRF	1 week	Updated ABC HSR eCRF
ALT≥3×ULN and bilirubin≥2×ULN (>35% direct) (or ALT≥3×ULN)	24 hoursc	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicabled	24 hours	Updated "SAE" data collection tool/"Liver Event" documents

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

a. Additional details and time frames for reporting supplementary information for cardiovascular and death events are provided in Section 8.5.7 and Section 8.5.8, respectively.
b. ABC HSR eCRF only required if event meets one of the ICH E2A definitions of seriousness.
c. GSK must be contacted at onset of liver chemistry elevations to discuss participant safety.
d. Liver event documents (i.e., "Liver Event eCRF" and updates, "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

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. Primary and

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.

8.5.7. Cardiovascular and Death Events

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

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

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 medical dictionary for regulatory activities (MedDRA) terms.

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

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

8.5.8. Death Events

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

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

8.6. 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 12.3. "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 8.5 and Section 12.4.

8.6.1. 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 ART medication is held due to toxicity or AEs, all ART medications should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each ART of the regimen, in order to minimize the risk of development of resistance.

No toxicity-related dose reductions of IP will be allowed. IP should be restarted as soon as medically appropriate; in general, for oral dosing, this should be no longer than 14 days after discontinuation (unless Grade 3 or 4 toxicities persist). Any interruption in therapy during the Maintenance Phase, oral dosing, of greater than 7 consecutive days must be discussed with and agreed by the Medical Monitor prior to resumption of therapy. The Medical Monitor must be contacted upon becoming aware of resumption in therapy, if therapy was resumed without prior approval (Section 6.8). **IM dosing is expected to occur during the month in which the participant's projected visit falls (as according to the first injection visit). An additional (+ or -) 7 day window, from the projected visit date, is stipulated for IM dosing.** Any interruption outside of this guidance MUST be discussed with the Medical Monitor prior to reinitiating IM IP (see Section 6.8.1).

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 6.7.1.1. 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 during the Long-Term Follow-Up (LTFU) Phase, in the event of a discontinuation of ABC for any reason, re-initiation 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 human leukocyte antigen *(HLA)-B*5701* status. Screening for the presence of *HLA-B*5701* is recommended prior to reinitiating treatment with ABC-containing products in participants of unknown *HLA-B*5701* status who have previously tolerated ABC but is not required to confirm study eligibility.

8.6.2. Grade 1 or Grade 2 Toxicity/Adverse Event

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

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

8.6.3. 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 LTFU 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 8.7.1). Isolated Grade 3 lipid abnormalities do not require withdrawal of IP.

8.6.4. 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 LTFU 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 8.7.1). 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.

8.7. Specific Toxicities/Adverse Event Management

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

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 8.5.3.

8.7.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event etiology during administration of study drug and the follow-up phase. All Phase 3 participants who meet liver stopping criteria will be adjudicated by the ViiV Safety and Labelling Committee (VSLC) – resulting in a case summary, adjudication, and management plan. The VSLC contains an external expert hepatologist, familiar with both DILI and cabotegravir, who will participate in this review. This committee meets on a 3-weekly basis, and can be convened on an ad hoc basis as needed.

8.7.2. Diarrhea

Participants with Grade 1 or 2 diarrhea may continue study intervention 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 LTFU 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.

8.7.3. Hypertriglyceridemia/ Hypercholesterolemia

Samples for lipid measurements **must** be obtained in a fasted state according to the Time and Events table (Section 8.1). 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.

8.7.4. Seizures

Four cases of seizures have occurred in the CAB program cumulatively through 04 May 2018.

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

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

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

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

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

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

8.8.2. Rationale for PK Sampling Strategy

Blood sampling for CAB, DTG and RPV concentrations will be performed during the course of the study to evaluate PK in HIV infected participants. The proposed PK visits and sampling scheme at each visit presented in Section 8.1 is based on consideration of available PK data to support interim and final PK analysis planned in this study.

8.8.3. Sample Analysis

8.8.3.1. CAB and DTG Sample Analysis

Plasma CAB and DTG analysis will be performed under the control of PTS-DMPK, GlaxoSmithKline, the details of which will be included in the SPM. Concentrations of CAB and DTG 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 and DTG, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK platform technology and science - drug metabolism and pharmacokinetics (PTS-DMPK), GSK protocol. No human deoxyribonucleic acid (DNA) analysis will be performed on these samples.

8.8.3.2. RPV Sample Analysis

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

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

8.9. Genetics

Information regarding genetic research is included in Section 12.6, Appendix 6: Genetic Research.

8.10. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide peripheral blood mononuclear cells (PBMCs) and plasma for storage samples according to the Time and Events Table (see Section 8.1) for potential viral genotypic and phenotypic analyses.

In addition, it allows for calculation of an 11-item scale score including the [redacted] item (item-[redacted]). The [redacted] item (item-[redacted] 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 HIV Dependent Quality of Life (HIVDQoL) is an individualised, self-completion questionnaire, specifically designed to measure quality of life in people living with HIV. The HIVDQoL was based on Audit of Diabetes-Dependent Quality of Life (ADDQoL) – a widely used questionnaire designed previously for participants with diabetes and linguistically validated in more than 60 languages (Bradley, 1999; Speight, 2001, Wee, 2006). The HIVDQoL includes two overview items, 26 condition-specific domain items and a free text box. The overview items ask participants to rate their generic 'present QoL' (7-point Likert scale, ranging from [redacted] to [redacted]) and HIV-specific 'impact of HIV on QoL' (5-point Likert scale, ranging from [redacted] to [redacted]).

The "Preference" question will contain a single item exploring whether participants prefer the CAB LA + RPV LA injectable to the oral CAB + RPV regimen administered in LATTE.

The "Reason for Switch" question will contain a single item exploring the reasons why participants are interested in switching to the CAB LA + RPV LA.

8.11.1. Value Evidence and Outcomes Endpoints (Secondary)

- Change from Baseline (Day 1) in total "treatment satisfaction" score, and individual item scores of the HIVTSQs at Months 6, 12 (or Withdrawal).
- Change in treatment satisfaction over time (using the HIVTSQc) at Month 12 (or Withdrawal).
- Change from Baseline (Day 1) in HIVDQoL at Months 6, and 12, (or Withdrawal).

8.11.2. Value Evidence and Outcomes Endpoints (Exploratory)

- The "Preference" question will be assessed in participants from LATTE, to assess preference for CAB LA + RPV LA Q2M to oral CAB + RPV regimen, at Month 12 using a single dichotomous preference question.
- The "Reason for Switch" question will be administered at Day 1 (Baseline) to assess the reasons for willingness to switch to LA injectable ART.

8.12. Digital Reminder

The Ensemble personalized health record tool by Epividian will be used to remind participants of their injection visits and administration of other medications. This would

be using a streamlined version of Ensemble that utilizes a combination of short message service (short message service [SMS] text messages) and small web pages that are loaded from links included in SMS messages. This product architecture of combined SMS and web pages allows a participant with virtually any smart phone to use the application, whereas a full-featured smart phone app would require support for specific operating systems and devices. Use of this tool is optional, but encouraged.

9. DATA MANAGEMENT

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

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

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

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

Please refer to Appendix 10 in Section 12.10 for study management information during the COVID-19 pandemic.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

No statistical hypotheses of treatment comparisons will be conducted within this study.

10.2. Sample Size Determination

Approximately 100 participants will be enrolled into this study from the LATTE study.

10.2.1. Sample Size Sensitivity

For the primary endpoint, antiviral response which will be assessed according the proportion of participants who have HIV-1 RNA ≥50 c/mL at Month 12, given the sample size of 100 participants and if the observed rate is around 3% then the upper bound of the 95% CI would be 6.3% (Table 6).

$C\tau$	Trough Concentration
CV	Cardiovascular
CVF	Confirmed Virologic Failure
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug-Drug Interaction
DILI	Drug induced liver injury
dL	Deciliter
DNA	Deoxyribonucleic acid
DRE	Disease-Related Events
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DTG	Dolutegravir, TIVICAY
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EFV	Efavirenz
EFV/TDF/FTC	Efavirenz/tenofovir disoproxil fumarate/emtricitabine
GFR	Glomerular filtration rate
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FRP	Females Of Reproductive Potential
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
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
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HIVDQoL	HIV Dependent Quality of Life
HIV TSQ	HIV treatment satisfaction questionnaire
HIV TSQ(c)	HIV treatment satisfaction questionnaire change version
HIV TSQ(s)	HIV treatment satisfaction questionnaire status version
HLA	Human leukocyte antigen
HR	Heart Rate
HRT	Hormone Replacement Therapy
HSR	Hypersensitivity reaction
IB	Investigator’s Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

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
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
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)

[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.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which 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.

12.4.2. Definition of SAE

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).

A SAE is defined as any untoward medical occurrence that, at any dose:
○ Results in death
○ Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization 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 outpatient setting. Complications that occur during hospitalization are AE. 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.

- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- 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 case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 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 causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

12.5.2. 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 7.

Table 7 Highly Effective Contraceptive Methods

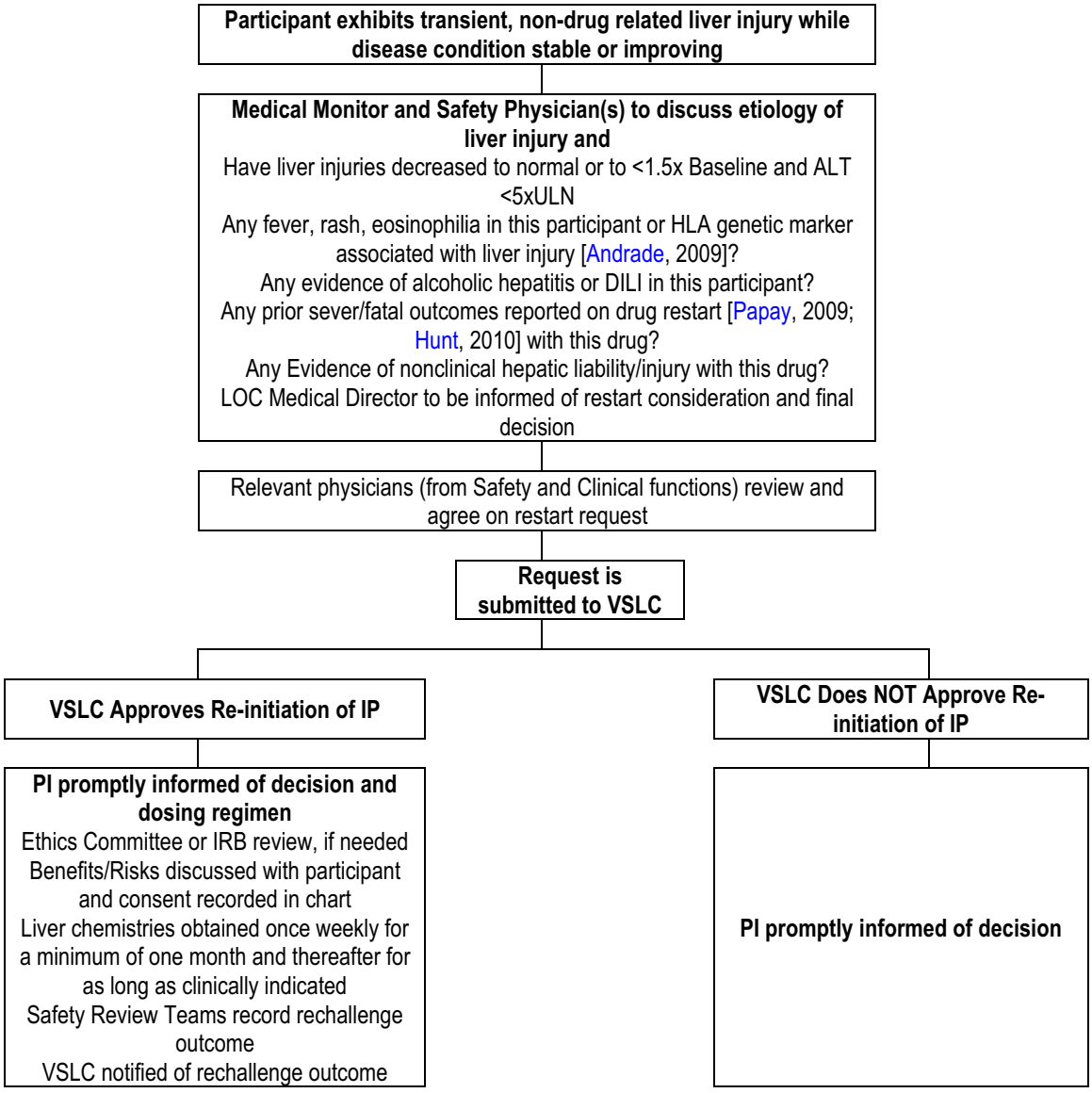
• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: 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 intervention. 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*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Figure 5 VSLC process for drug restart approval or disapproval



12.7.4. Medical monitor, GCSP Physician and PI actions for Restart or Rechallenge following VSLC decision

12.7.4.1. 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

authorised/accredited local laboratory (or other relevant clinical facility), if this can be done within local restrictions on physical distancing. The site should proactively inform the sponsor about such instances. Local laboratory results may be used to inform safety decisions. Results should be retained in source records.

- When on-site visits are reduced, it is important that the investigator continue collecting relevant clinical information, including adverse events, from the participant through alternative means, e.g. by telephone contact.
- There may be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.
- There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, in order to protect a study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations.

12.10.2. Changes to Informed Consent

Informed consent should continue per normal procedure and as described in the main body of the protocol, to the extent possible. However, there may be circumstances where re-consent of participants is needed, and a physical signature on site is not possible. In these cases, alternative ways of obtaining such re-consent should be considered, such as the participant sending a picture of his/her written consent to the investigator, or the investigator contacting the participant by telephone or video call and obtaining verbal consent, supplemented with email confirmation.

Any updated informed consent form or other subject-facing materials should be provided to participants by e-mail, mail or courier before re-consent is obtained. Any consent obtained this way should be documented in source records and confirmed by way of normal consent procedure at the earliest opportunity when participants attend their next on-site study visit.

Any alternative informed consent procedure must be undertaken only after site IRB/Ethics Committee agreement and approval.

12.10.3. Permissible Use of Antiretroviral Therapy

In order to minimize the risk of gaps in HIV-1 antiretroviral therapy (ART) for participants impacted by COVID-19 in the clinical trial, the following options can be considered with regards to ART dosing, in order of preference:

Objectives	Endpoints
To assess participant reported health-related quality of life, injection tolerability/acceptability, and treatment satisfaction.	Change from Baseline (Day 1) in HIV dependent quality of life (HIVDQoL) at Months 6 and 12 (or Withdrawal) Change from baseline (Day 1) in total "treatment satisfaction" score, and individual item scores of the HIV Treatment Satisfaction Status Questionnaire (HIVTSQs) at Months 6 and 12 (or Withdrawal) Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire (HIVTSQc) at Month 12 (or Withdrawal).
Exploratory	
Explore the concept of a digital assistance program and the effect on participant participation and adherence to timeliness of injections given every 2 months	The number of participants who utilize the program Adherence to scheduled date of injection
To assess reason for switching using a single question. To assess preference using a single question	The 'Preference" question will be used to assess preference for CAB LA + RPV LA every 2 months compared to prior oral CAB + RPV regimen, at Month 12 using a single dichotomous preference question. The "Reason for Switch" question will be administered at Day 1 (Baseline) to assess the reasons for willingness to switch to LA injectable ART.

Overall Design:

Study 209035 (POLAR) is a Phase IIb, open-label, multicenter rollover study designed to assess the antiviral activity and safety of CAB LA + RPV LA administered every 2 months in approximately 100 adult HIV-1 infected participants from the LATTE study.

Participants who fulfill eligibility requirements will be entered into the study to receive either CAB LA + RPV LA Q2M or the oral DTG + RPV regimen for at least 12 months, until commercially available.

Participants currently receiving oral CAB + RPV within LATTE will enter POLAR at Day 1 and choose to either transition to Q2M administration of injectable CAB LA +

Procedures Q2M	**Day 1** [a]	**Month**													**WD** [l, m]
		2 [o]	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**[b]	**22**[b]	**24**	**26**	
Fasting Glucose, Cholesterol (Total, high density lipoprotein [HDL] and low density lipoprotein [LDL]) and Triglycerides [i]	X						X						X		X
Prothrombin time (PT)/ partial thromboplastin time (PTT)/international normalized ratio (INR)	X														X
PK Diary (D)ispensation and (R)eview	R														
PK Sample (S)torage [j]	S						S								S
LA Study Intervention Administration [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIVTSQc							X								X
HIVTSQs	X			X			X								X
HIVDQoL	X			X			X								X
Preference							X								
Reason for Switch	X														

Objectives	Endpoints
	12 (or Withdrawal).
Exploratory	
Explore the concept of a digital assistance program and the effect on participant participation and adherence to timeliness of injections given every 2 months	The number of participants who utilize the program Adherence to scheduled date of injection
To assess reason for switching using a single question. To assess preference using a single question	The 'Preference" question will be used to assess preference for CAB LA + RPV LA every 2 months compared to prior oral CAB + RPV regimen, at Month 12 using a single dichotomous preference question. The "Reason for Switch" question will be administered at Day 1 (Baseline) to assess the reasons for willingness to switch to LA injectable ART.

4. STUDY DESIGN

4.1. Overall Design

Study 209035 (POLAR) is a Phase IIb, open-label, multicenter rollover study designed to assess the antiviral activity and safety of CAB LA + RPV LA administered every 2 months in approximately 100 adult HIV-1 infected participants from the LATTE study.

Participants who fulfill eligibility requirements will be entered into the study to receive CAB LA + RPV LA Q2M or the oral DTG + RPV regimen for at least 12 months, until commercially available.

Participants currently receiving oral CAB + RPV within LATTE will enter POLAR at Day 1 and choose to either transition to Q2M administration of injectable CAB LA + RPV LA or take oral DTG + RPV daily for 12 months. Eligible participants include those originally randomized to oral CAB + RPV in the Maintenance phase and transitioned to the Extension Phase of LATTE. The first injection visit for POLAR can be performed once the most recent central lab results from LATTE are available and safety parameters have been reviewed, and the LATTE Week 312 visit (close-out visit) has been completed (or Week 324 in the event of unavoidable delays). Participants will continue to receive oral CAB + RPV as scheduled within the LATTE trial until their eligibility for POLAR can be fully evaluated and the participant has chosen the new regimen. If determined to be ineligible for POLAR or participant elects to not participate in the study those participants will be withdrawn from the LATTE study.

CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). The second loading injections will be administered 1 month (Month 2 visit, start of the second month of the study) after initial loading dose (CAB LA 600 mg + RPV LA 900 mg), with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring every 2 months thereafter. The dosing window for the second injection will be -7 days from the projected dosing visit.

After Month 2, a dosing window (±7 days) for injections is stipulated. Doses outside of the window may be allowed with Medical Monitor approval.

Participants will continue CAB LA + RPV LA until:

- study intervention is locally approved and commercially available,
- the participant no longer derives clinical benefit,
- the participant meets a protocol-defined reason for discontinuation
- the development of either CAB LA or RPV LA is terminated.

Safety and efficacy assessments will be conducted as per the Time and Events schedule (Section 8.1 for more information). Dosing will occur according to the selected regimen.

If the IM dosing regimen (Q2M) is discontinued as a result of an independent data monitoring committee (IDMC) from another study evaluating the same regimen, review any subsequent analysis, or any other programmatic analysis, those participants who have not met any clinical management criteria for discontinuation will be discontinued permanently from the study and will enter into the long-term follow-up (LTFU) Phase of the study.

4.2.2.1. Participants electing to receive oral DTG + RPV once daily

The DTG + RPV oral regimen will be administered in an open-label fashion starting on Day 1 until Month 12. Participants will continue study intervention until:

- study intervention is locally approved and commercially available,
- the participant no longer derives clinical benefit,
- the participant meets a protocol-defined reason for discontinuation

Safety and efficacy assessments will be conducted as per the Time and Events schedule (Section 8.1 for more information). Dosing will occur according to the selected regimen.

4.2.3. LTFU Phase – IM Regimen Only

Any participant who receives at least one dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. **Investigators must discuss the choice of the follow-up HAART regimen with the Medical Monitor prior to initiating the new regimen with the participant. HAART therapy should be initiated within 8 weeks after the last Q2M injection, however if withdrawn due to virologic failure, HAART should be initiated as soon as virologic**

4.4. Justification for Dose

4.4.1. Long Acting Injectable for Maintenance Phase

LATTE demonstrated that a 2-drug, 2-class regimen could safely maintain virologic suppression with oral CAB and RPV, which informed CAB LA and RPV LA dose selection for the Phase 2b study 200056 (LATTE-2). LATTE-2 is currently ongoing with two dosing regimens of CAB LA + RPV LA given Q4W or Q8W. Following a 20-week Induction Phase (16 weeks of oral CAB + 2 NRTIs, 4 weeks of CAB + 2 NRTIs + oral RPV), participants who were eligible to continue into the Maintenance Phase were then randomized (2:2:1) to receive IM injections of CAB LA Q4W (800 mg Day 1 then 400 mg Q4W)) or Q8W (800 mg Day 1, 600 mg Week 4, 600 mg Week 8, then 600 mg Q8W) in combination with IM RPV LA Q4W (600 mg Day 1 then 600 mg Q4W) or Q8W (900 mg Day 1, 900 mg Week 8, then 900 mg Q8W), respectively, or to continue on their triple ART regimen.

The Q4W dosing strategy was selected for further investigation in Phase 3 based on observed viral suppression, safety, and tolerability at Week 48. Both Q4W and Q8W regimens were continued throughout the Maintenance Phase of LATTE-2 as planned, and Week 96 results (Table 1) were supportive of further evaluation of the Q2M regimen in the present study. Moreover, LATTE-2 was amended to permit participants to remain on their randomized LA regimen (either Q4W or Q8W) during the Extension Phase (post Week 96), and those participants randomized to the oral comparator arm were allowed transition to either LA regimen at Week 96. Forty-four participants were transitioned from the oral comparator arm to LA treatments in the Extension Phase; 34 (77%) opted for the Q8W regimen and 10 (23%) for the Q4W regimen. Initial LA injections for these subjects were administered at Week 100.

Table 1 Summary of Study Outcomes (<50 copies/mL) at Weeks 48 and 96 – Snapshot (MSDF) Analysis (ITT-ME Population) in LATTE-2

Endpoint (Week)	Outcome	Q8W IM N=115 n (%)	Q4W IM N=115 n (%)	CAB 30 mg+ ABC/3TC N=56 n (%)	Subtotal IM N=230 n (%)
W48	Virologic Success, n (%)	106 (92)	105 (91)	50 (89)	211 (92)
	Virologic Failure, n (%)	8 (7)	1 (<1)	1 (2)	9 (4)
W96	Virologic Success, n (%)	108 (94)	100 (87)	47 (84)	208 (90)
	Virologic Failure, n (%)	5 (4)	0	1 (2)	5 (2)

The CAB LA population PK model was updated to include data from CAB LA pre-exposure prophylaxis (PrEP) Study 201120 (ÉCLAIR; GlaxoSmithKline Document Number 2016N269422_00) and Study 200056 (LATTE-2), increasing the original model from 93 participants to 416 participants receiving CAB LA single or repeat IM injections. Modeling and simulation was used to enable simplification and alignment of loading dose strategy used in LATTE-2 for both Q4W and Q8W CAB LA and RPV LA dosing regimens, resulting in selection of optimized loading dosing strategy for use in the Extension Phase of LATTE-2 and Phase 3 studies. The Phase 3 studies FLAIR and ATLAS adopted a monthly (QM) dosing strategy with a regimen of CAB LA 600 mg IM and RPV LA 900 mg IM as initial loading doses followed by CAB LA 400 mg IM and RPV LA 600 mg IM QM. Based on positive results from the Week 96 analysis of

4.4.1.2. RPV LA Q2M

The RPV LA Q2M regimen for this study (POLAR) was selected based on safety and efficacy data from study 200056 (LATTE-2) and supported by modeling and simulation of pharmacokinetic data obtained following administration RPV LA administration in healthy participants (Phase 1 studies C158, and LAI115428 [GlaxoSmithKline Document Number 2011N112455_03]) and in HIV-infected participants (Phase 2 study LATTE-2), the majority of the data coming from 200056 (LATTE-2).

The RPV LA 900 mg Q2M regimen is predicted to achieve median (90% PI) steady-state Cτ of 54 ng/mL (23 – 112 ng/mL) (Figure 3). With this regimen, 100% of participants remain above the RPV protein-adjusted 90% inhibitory concentration (PA-IC_{90}) during the whole dose interval at steady-state. These data are similar to the observed Week 32 median steady-state Cτ in LATTE-2 for Q8W which was also 54 ng/mL and the mean Cτ was 58 ng/mL. The RPV LA Q2M regimen consists of identical 900 mg doses administered at Day 1, Month 2, and Q2M thereafter. With the second RPV LA dose administered 1 month after the first dose, the anticipated median RPV Cτ at Week 4 (prior to second injection) is 40 ng/mL (versus 30 ng/mL observed prior to second injection at Week 8 in LATTE-2, where the RPV LA dose at Week 4 was not included), with >92% of participants above the RPV PA-IC_{90} of 12 ng/mL. Observed data for the optimized Q2M regimen in LATTE-2 Extension Phase were consistent with predictions, with a geometric mean RPV trough concentration of 49.9 ng/mL 4 weeks following the 900 mg IM loading dose and of 57.5 ng/mL following the fourth injection.

Procedures Q2M	**Day 1 [a]**	**Month**													**WD [l, m]**
		2 [o]	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20[b]**	**22[b]**	**24**	**26**	
PK Diary (D)ispensation and (R)eview	R														
PK Sample (S)torage j	S						S								S
LA Study intervention Administration [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIVTSQc							X								X
HIVTSQs	X			X			X								X
HIVDQoL	X			X			X								X
Preference							X								
Reason for Switch	X														
Participant Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

See footnote "b" for continuation of visit schedule after Month 26. Continue until either locally approved and commercially available, the participant no longer derives clinical benefit or meets a protocol-defined reason for discontinuation or until development is terminated.

8.1.3. Time and Events Table for Long Term Follow Up

Procedures for Long-Term Follow Up	Month 1 [a]	Month 3	Month 6	Month 9	Month 12	WD	Notes
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	Every effort should be made to enter participants into the Long-Term Follow Up if they withdraw from or discontinue the study after receiving at least one dose of CAB LA and / or RPV LA. a) The start of the 52-week follow up period begins the day of the last CAB LA and/or RPV LA dose. b) Women of childbearing potential only. S = Serum c) Fast overnight; however, a minimum of a 6 hour fast is acceptable. d) Women of childbearing potential should continue to receive counselling on the need to use adequate contraception for the entirety of the Long-Term Follow-Up Period. e) **Investigators must discuss choice of HAART regimen and timing of initiation with the medical monitor before initiating. This regimen may be supplied regionally by GSK or reimbursement will be provided.**
HIV-1 RNA	X	X	X	X	X	X	
CD4+	X	X	X	X	X	X	
Plasma for Storage	X	X	X	X	X	X	
PK Sample for Storage	S	S	S	S	S	S	
Clinical Chemistry and Hematology	X	X	X	X	X	X	
Pregnancy Testing [b]	S	S	S	S	S	S	
Urinalysis	X				X	X	
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [c]					X	X	
PT/PTT/INR					X	X	
Contraception Counselling [d]	X	X	X	X	X	X	
HAART Dispensation [e]	X	X	X	X	X	X	

Table 3 Safety Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[c]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine clearance[b]
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			
Plasma HIV-1 RNA[e]			
CD4+ and CD8+ cell counts [CD4/CD8 ratio][f]			
Peripheral Blood Mononuclear Cells (PBMCs): Day 1 and Withdrawal only			
Rapid Plasma Reagin (RPR)			
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)			
Pregnancy test for women of childbearing potential[g]			
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate			
Genetics Sample			
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)			

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

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [Levey, 2009].
c) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
d) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
e) For participants meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain genotype/phenotype data.
f) CD8+ cells will only be reported at Baseline, Day 1, Months 12 and end of the study.
g) Urine pregnancy test/ serum pregnancy test will be performed according to the Time and Events Table (Section 8.1).

8.4.3. Physical Examinations

Physical exams should be conducted as part of normal routine clinical care. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems.

suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

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

8.4.7. Pregnancy

8.4.7.1. Pregnancy testing

Women of childbearing potential must have a negative pregnancy test at Screening, and at Baseline (Day 1). Pregnancy testing will also be conducted as per the Time and Events Table (Section 8.1) and at any time 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.

8.4.7.2. Time Period for Collecting Pregnancy Information

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

Female participants that have received at least one dose of CAB LA or RPV LA and do not enter the LTFU Phase should use a highly-effective method of contraception (see the SPM and Appendix 5 (Section 12.5) for a listing of examples of highly-effective 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.

8.4.7.3. Action to be Taken if Pregnancy Occurs

Any individual who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study and must immediately discontinue study drug. Participants who have received at least one dose of CAB LA and/or RPV LA should discontinue further dosing and continue oral HAART in the LTFU Phase (see Section 4.2.3 above), 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 Section 12.5, Appendix 5.

secondary Medical Monitor/SAE contact information is provided on the Medical Monitor/Sponsor Information Page of the current protocol.

8.5.5. 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 12.8) can be serious/life threatening and will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE. However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The investigator determines that the event or outcome qualifies as an SAE under part 'other situations' of the SAE definition (see Section 12.4.2), or
- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

If any of the above conditions is met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly (i.e., expedited reporting, see Section 8.5.4) to GSK.

8.5.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study intervention (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.

The Sponsor 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, IRB/ IEC and investigators.

8.7.5. Creatine Phosphokinase (CPK) Elevation

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

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

8.7.6. 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 LTFU Phase for 52 weeks of **follow up.**

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

Approval by VSLC for drug restart can be considered where:

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

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

8.10.1. HIV-1 Polymerase Viral Genotyping and Phenotyping

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

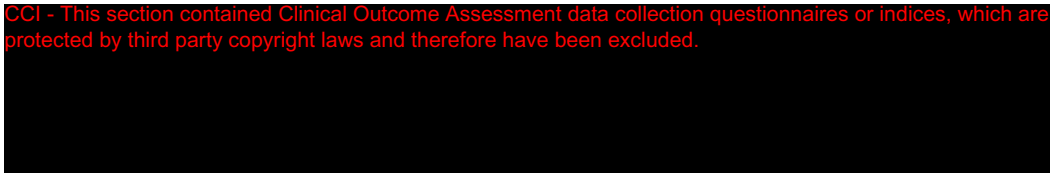
8.10.2. HIV-1 Exploratory Analysis

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

8.11. Value Evidence and Outcomes

Health outcomes assessments will be conducted according to the Time and Events Table (Section 8.1). Assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments.

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:

- CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
- 

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 the 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).

Table 6 Precision in Estimation According to Sample Size and Observed Proportion with HIV-1 RNA ≥50 c/mL

Sample Size	Observed Proportion HIV-1 RNA ≥ 50 c/mL	Upper limit of 95% Confidence Interval †
90	2%	4.9%
100	2%	4.7%
110	2%	4.6%
90	3%	6.5%
100	**3%**	**6.3%**
110	3%	6.2%
90	4%	8.0%
100	4%	7.8%
110	4%	7.7%

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

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the informed consent form (ICF)
Safety	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. This population will be used for all summaries unless otherwise specified.

10.4. Statistical Analyses

Endpoint	Statistical Analysis Methods
Primary	Descriptive summaries of the proportion of participants with plasma HIV-1 RNA ≥50 c/mL as per FDA Snapshot algorithm at Month 12.
Secondary	Descriptive summaries of the following secondary efficacy endpoints will be produced: Proportion of participants with plasma HIV-1 RNA <50 c/mL (c/mL) at Month 12 using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] population) Proportion of participants with protocol-defined confirmed virologic failure (CVF) through over time Proportion of participants with HIV-RNA greater than or equal to 50 c/mL as per FDA Snapshot algorithm overtime Absolute values and changes from Baseline in viral load and CD4+ cell counts

IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
INH	Isonicotinylhydrazid
INI	Integrase inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT-ME	Intent-to-Treat Maintenance Exposed
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
ISR	Injection Site Reaction
IV	Intravenous
Kg	Kilogram
LA	Long Acting
LATTE	**L**ong **A**cting an**T**iretroviral **T**reatment **E**nabling Study
LATTE-2	**L**ong **A**cting an**T**iretroviral **T**reatment **E**nabling Study - 2
LDH	Lactate Dehydrogenase
LDL	Low density lipoprotein
LLOD	Lower Limit Of Detection
LOC	Local Operating Company
LTFU	Long-Term Follow-UP
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
meq	Milliequivalence
MDL	Medicines Development Leader
Mg	Milligram
Mg/dL	Milligram
mmol	Millimolar
MSDS	Material Safety Data Sheet
msec	Milliseconds
µg	Microgram
ng	Nanogram
NOAEL	No-Observed-Adverse-Effect-Level
NNRTI	Non-Nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OCT-2	Organic cation transporter
PA-IC90	Protein-Adjusted 90% Inhibitory Concentration
PBMCs	Peripheral Blood Mononuclear Cells
PDVF	Protocol-defined virologic failure
PI	Protease inhibitor
PK	Pharmacokinetic
PO	Per-oral

Cardiovascular

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

[2] As per Bazett's formula.

Results in persistent disability/incapacity

- 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

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]

12.5.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- 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 participant and neonate, 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 for medical reasons 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 intervention by the investigator, will be reported to GSK as described in Appendix 4 (Section 12.4). 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 female participant who becomes pregnant while participating

- will discontinue study intervention or be withdrawn from the study

Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

12.7.4.2. 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 participant 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 participant's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed ***twice weekly for 'rechallenge' cases*** and ***once weekly for 'restart' cases*** for a minimum of one month and thereafter for as long as clinically indicated following drug re-initiation. If participant exhibits protocol-defined liver chemistry elevations, IP should be discontinued as protocol specified.
- Medical Monitor and the Ethics Committee or Institutional Review Board must be informed of the participant's outcome following drug rechallenge or restart.

Drug Rechallenge or Drug Restart Outcomes Table Template

To be completed/updated and provided to VSLC with each event recorded across studies and indications

Drug Rechallenge/Restart Outcomes Table – Update with each event

Protocol#	Participant#	Rechallenge or Restart?	Safety outcome*	Drug benefit

Rechallenge/restart safety outcomes:

0 = no liver chemistry elevation

1 = recurrent liver chemistry elevation not meeting participant stopping criteria

2 = recurrent liver chemistry elevation meeting participant stopping criteria

3 = serious adverse event

4 = fatality

1. Where possible, and safe to do, please continue to prioritize IM dosing visits in order to keep the participants on the protocol-defined regimen

    a. Qualified healthcare professionals (HCPs) trained on study procedures can administer IM injections outside of the study clinic setting (e.g. home, nursing facility, hospital), assuming this can be done safely, without compromising investigational product preparation/handling/storage/accountability requirements and done in accordance with local requirements. Please seek approval by the study team on a case-by-case basis.

2. If a participant is not able to attend an IM injection visit due to COVID-19 related restrictions, the gap in IM dosing should be covered with oral ART, until IM dosing can resume. Participants should be reminded of the importance of adhering with daily oral dosing. Two options can be approved for oral bridging therapy in consultation with the Medical Monitor, listed in order of preference:

    a. Oral CAB + RPV
        i. Investigator should request availability of oral CAB + RPV supplies, prior to pursuing option b.
    b. Oral standard of care (SOC) commercial ART (prescribed locally)

<u>Oral bridging with CAB + RPV</u>

The protocol permits oral bridging to cover planned missed injections with oral CAB + RPV, only until IM dosing can be resumed. The start date of oral bridging should be within the dosing window for the missed IM dosing visit. This recommendation can be used to accommodate requests for oral dosing due to COVID-19. Oral bridging recommendations should be followed as per protocol Section 6.7.1.1. The process and required information for requesting oral bridging can be found in your Study Reference/Procedure Manual. Please continue to reach out to your study medical monitor for approval of oral bridging, in order to document use and to ensure expeditious shipment of oral CAB + RPV to your site.

Participants who use oral CAB + RPV as short-term oral bridging are permitted to return to IM dosing, on protocol, once the COVID-19 conditions permit resumption of site activities.

The investigator should reach out to the medical monitor to confirm IM restart instructions, and to ensure the participant remains appropriate for resumption of IM dosing. If oral bridging with CAB/RPV is anticipated to continue for > 2 months, additional approval and guidance should be obtained from the medical monitor to continue with oral bridging therapy. Loading/Re-initiation doses of CAB + RPV IM may be required, depending on the length of oral bridging.