beginning with 4 weeks of oral lead-in with CAB + RPV to confirm tolerability prior to IM dosing with CAB LA and RPV LA. Eligible participants entering from ATLAS on the CAB LA+ RPV LA Q4W regimen will be randomized (1:1) to either continue Q4W injections or transition to Q8W injections in ATLAS-2M (without the oral lead-in).

All participants who successfully complete Week 100 of CAB LA + RPV LA treatment in the Maintenance Phase will continue to have access to their randomized CAB LA + RPV LA regimen in the Extension Phase until CAB LA and RPV LA are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of their assigned CAB LA + RPV LA regimen is terminated.

1.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every 8 weeks (every two months) compared to CAB LA + RPV LA every 4 weeks (monthly) over 48 weeks in suppressed HIV-1 infected antiretroviral therapy (ART)-experienced participants	Proportion of participants with plasma HIV-RNA greater than or equal to 50 copies/mL as per Food and Drug Administration (FDA) Snapshot algorithm at Week 48 (Intent-to-Treat Exposed [ITT-E] population)
Secondary	
To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks	Proportion of participants with plasma HIV-1 RNA <50 c/mL (c/mL) at Week 24, Week 48 and Week 96 using the FDA Snapshot algorithm (Intent-to-Treat Exposed [ITT-E] population) Proportion of participants with protocol-defined confirmed virologic failure (CVF) through Week 24, Week 48 and Week 96 Proportion of participants with HIV-RNA greater than or equal to 50 c/mL as per FDA Snapshot algorithm at Week 24 and Week 96 Absolute values and changes from Baseline in viral load and CD4+ cell counts over time including Week 48 and Week 96

Objectives	**Endpoints**
To evaluate the safety and tolerability of CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks	Incidence and severity of AEs and laboratory abnormalities over time including Week 24, Week 48 and Week 96 Proportion of participants who discontinue treatment due to AEs over time including Week 24, Week 48 and Week 96 Change from Baseline in laboratory parameters over time including Week 48 and Week 96
To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV through Week 24, Week 48 and Week 96
To characterize CAB and RPV concentrations and population pharmacokinetics and identify important determinants of variability	Plasma PK parameters for CAB LA and RPV LA (when evaluable, $C_{trough,}$ concentrations post dose [~Cmax], and area under the curve [AUC]) Demographic parameters including, but not limited to, age, sex, race, body weight, body mass index, and relevant laboratory parameters will be evaluated as potential predictors of inter- and intra-participant variability for pharmacokinetic parameters
To assess preference for CAB LA + RPV LA every 8 weeks or CAB LA + RPV LA every 4 weeks LA compared to oral antiretroviral (ARV) To assess preference for CAB LA+ RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks	Preference for CAB LA + RPV LA every 8 weeks and CAB LA + RPV LA every 4 weeks compared to oral ARV and preference for CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks will be assessed using a preference questionnaire at week 48 (or Withdrawal).
To assess patient reported health-related quality of life, treatment satisfaction, injection tolerability, and treatment acceptance.	Change from Baseline (Day 1) in HRQoL at Week 24, and Week 48 (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 Week 24, and 48, (or Withdrawal)

Group 2: Patients currently receiving CAB LA + RPV LA Q4W

Patients currently receiving CAB LA + RPV LA Q4W within ATLAS will be randomized at Day 1 to either continue Q4W administration or transition to Q8W administration of CAB LA + RPV LA. Eligible patients include those originally randomized to Q4W in the Maintenance phase of ATLAS and those who transitioned from SOC to the Q4W regimen within the Extension Phase of ATLAS. The first injection visit for ATLAS-2M can be performed once the final central lab results from ATLAS are available and safety parameters have been reviewed, and the ATLAS Week 52 visit (at minimum) has been completed. Participants will continue to receive CAB LA + RPV LA Q4W injections as scheduled within the ATLAS trial until their eligibility for ATLAS-2M can be fully evaluated and the participant is re-randomized (Q4W or Q8W). If determined to be ineligible for ATLAS-2M, those participants can elect to continue participation in ATLAS or withdraw from the ATLAS study.

Participants in ATLAS-2M who successfully complete Week 100 (without meeting study defined withdrawal criteria) will be given the option to continue to receive their randomized treatment (CAB LA + RPV LA administered Q4W or Q8W) in the Extension Phase until the randomized study treatment 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 Q4W and/or Q8W is terminated. Alternatively, participants can choose to complete study participation and enter the 52-week Long-Term Follow-Up (LTFU) Phase of the study.

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

In order to achieve balance across the treatment arms, randomization will be stratified by prior CAB + RPV Exposure: 0 weeks, 1-24 weeks, >24 weeks. The primary endpoint for the study is the proportion of participants with HIV-RNA greater than or equal to 50 c/mL (Virologic Failure) at Week 48 as per Food and Drug Administration (FDA) Snapshot algorithm using the Intent-to-Treat Exposed (ITT-E) population. The proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, ITT-E population) is a key secondary endpoint comparison.

The sample size of 1020 provides 85% power to demonstrate non-inferiority in the primary endpoint at Week 48 using a 4% margin, assuming a true 3% failure rate for Q8W CAB LA + RPV LA and a 2% failure rate for the Q4W CAB LA + RPV LA arm and a 2.5% one-sided alpha level (using unpooled Z test statistic).

1.4. Treatment Groups and Duration

1.4.1. Screening Phase (Up to 35 days)

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

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

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

1.4.2. Maintenance Phase (Day 1 up to Week 100)

There are two ways in which study participants may transition to the LA regimen, either directly from oral SOC or from Q4W dosing from ATLAS.

The Table and Figure below describe the CAB LA + RPV LA dosing regimens in ATLAS-2M based on the mode of transition.

CAB LA + RPV LA Dosing Regimens in ATLAS-2M

Participants Transitioning from Oral Standard of Care (SOC)		
Regimen	**CAB LA**	**RPV LA**
Q4W	CAB LA: Week 4b: 600 mg (Loading Dose) Week 8 & Q4W thereafter: 400 mg	RPV LA: Week 4b: 900 mg (Loading Dose) Week 8 & Q4W thereafter: 600 mg
Q8W	CAB LA: Week 4b, Week 8, & Q8W thereafter: 600 mg	RPV LA: Week 4b, Week 8, & Q8W thereafter: 900 mg
Participants Transitioning from ATLAS Q4W		
Regimen	**CAB LA**	**RPV LA**
Q4W	CAB LA: Day 1 & Q4W thereafter: 400 mg	RPV LA: Day 1 & Q4W thereafter: 600 mg

Objectives	**Endpoints**
To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV through Week 24, Week 48 and Week 96
To characterize CAB and RPV concentrations and population pharmacokinetics and identify important determinants of variability	Plasma PK parameters for CAB LA and RPV LA (when evaluable, $C_{trough,}$ concentrations post dose [~Cmax], and area under the curve [AUC]) Demographic parameters including, but not limited to, age, sex, race, body weight, body mass index, and relevant laboratory parameters will be evaluated as potential predictors of inter- and intra-participant variability for pharmacokinetic parameters
To assess preference for CAB LA + RPV LA every 8 weeks or CAB LA + RPV LA every 4 weeks LA compared to oral antiretroviral (ARV) To assess preference for CAB LA+ RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks	Preference for CAB LA + RPV LA every 8 weeks or CAB LA + RPV LA every 4 weeks compared to oral ARV and preference for CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks will be assessed using a preference questionnaire at week 48 (or Withdrawal).
To assess patient reported health-related quality of life, treatment satisfaction, injection tolerability, and treatment acceptance.	Change from Baseline (Day 1) in HRQoL at Week 24, and Week 48 (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 Week 24, and 48, (or Withdrawal) Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire HIVTSQc at Week 48 (or Withdrawal). Change from Week 8 in Dimension scores ("Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of

the final central lab results from ATLAS are available and safety parameters have been reviewed.

Group 2: Patients currently receiving CAB LA + RPV LA Q4W

At Day 1, patients entering ATLAS-2M from ATLAS and currently receiving CAB LA + RPV LA Q4W (including both those who were originally randomized to Q4W in the Maintenance phase of ATLAS and those who transitioned from SOC to the Q4W regimen within the Extension Phase of ATLAS) will be randomized 1:1 to either continue Q4W administration or transition to Q8W administration of CAB LA + RPV LA. The first injection visit for ATLAS-2M can be performed once the final central lab results from ATLAS are available and safety parameters have been reviewed, and the ATLAS Week 52 visit (at minimum) has been completed. Participants will continue to receive CAB LA + RPV LA Q4W injections as scheduled within the ATLAS trial until their eligibility for ATLAS-2M can be fully evaluated and the participant is re-randomized (Q4W or Q8W). If determined to be ineligible for ATLAS-2M, those participants can elect to continue participation in ATLAS or withdraw from the ATLAS study.

Participants in ATLAS-2M who successfully complete Week 100 (without meeting study defined withdrawal criteria) will be given the option to continue to receive their randomized treatment (CAB LA + RPV LA administered Q4W or Q8W) in the Extension Phase until the randomized study treatment 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 Q4W and/or Q8W is terminated. Alternatively, participants can choose to complete study participation and enter the 52-week LTFU Phase of the study.

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

In order to achieve balance across the treatment arms, randomization will be stratified by prior CAB + RPV Exposure: 0 weeks, 1-24 weeks, >24 weeks. The primary endpoint for the study is the proportion of participants with HIV-RNA greater than or equal to 50 c/mL (Virologic Failure) at Week 48 as per Food and Drug Administration (FDA) Snapshot algorithm using the Intent-to-Treat Exposed (ITT-E) population. The proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, ITT-E population) is a key secondary endpoint comparison.

The sample size of 1020 provides 85% power to demonstrate non-inferiority in the primary endpoint at Week 48 using a 4% margin, assuming a true 3% failure rate for Q8W CAB LA + RPV LA and a 2% failure rate for the Q4W CAB LA + RPV LA arm and a 2.5% one-sided alpha level.

4.2.2. Maintenance Phase (Day 1 up to Week 100)

There are two ways in which study participants may transition to the LA regimen, either directly from oral SOC or from Q4W dosing from ATLAS.

Table 1 and Figure 2 describe the CAB LA + RPV LA dosing regimens in ATLAS-2M based on the mode of transition.

Table 1 CAB LA + RPV LA Dosing Regimens in ATLAS-2M

Participants Transitioning from Oral Standard of Care (SOC)		
Regimen	**CAB LA**	**RPV LA**
Q4W	CAB LA: Week 4b: 600 mg (Loading Dose) Week 8 & Q4W thereafter: 400 mg	RPV LA: Week 4b: 900 mg (Loading Dose) Week 8 & Q4W thereafter: 600 mg
Q8W	CAB LA: Week 4b, Week 8, & Q8W thereafter: 600 mg	RPV LA: Week 4b, Week 8, & Q8W thereafter: 900 mg
Participants Transitioning from ATLAS Q4W		
Regimen	**CAB LA**	**RPV LA**
Q4W	CAB LA: Day 1 & Q4W thereafter: 400 mg	RPV LA: Day 1 & Q4W thereafter: 600 mg
Q8W	CAB LA: Day 1 & Q8W thereafter: 600 mg	RPV LA: Day 1 & Q8W thereafter: 900 mg
All participants entering ATLAS-2M from an oral SOC regimen will receive a 4-week oral lead-in of CAB+RPV prior to receiving IM injections, except for ATLAS subjects transitioning from Q4W to Q8W injections. These participants previously established safety and tolerability of CAB + RPV within the ATLAS study.		

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 Q4W regimen is currently under evaluation in the ongoing Phase III ATLAS study.

The open-label design best suits the objectives of this study. A double-dummy design could not be undertaken given the logistical challenges of blinding each regimen. Because 2 injections of each investigational product are administered at every visit, a double-dummy design would require all subjects to chronically receive 4 injections per Q4W visit (2 active and 2 placebo), which could be intolerable for patients. In addition, the volume of CAB LA and RPV LA injections will differ significantly between Q8W and Q4W IM injections (3 mL vs 2 mL each), it would not be logistically feasible to blind site staff nor patients from the study treatments being administered.

Participants randomized to receive CAB LA + RPV LA Q8W IM administration will be required to participate in clinic visits approximately every 8 weeks while participants randomized to receive Q4W IM administration will be required approximately monthly clinical visits. Importantly, secondary objectives of this study are to understand the acceptability, tolerability, and patient reported preferences to these novel injectable regimens. 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 Q8W arm were required to receive blinded placebo injections every month, the value of comparing safety, tolerability, and convenience of Q8W compared to Q4W administrations would be limited and include overly burdensome visit requirements for those randomized to Q8W administration. Additionally, the perceived value for participants to transition from the ATLAS study to ATLAS-2M for potential randomization to the Q8W regimen would also be limited and may result in loss of patients with prior Q4W experience, thereby limiting the ability to compare experience of Q4W and Q8W regimens within individual patients.

Due to the complexities, lack of feasibility and limitations of blinding CAB LA and RPV LA injections for Q8W compared to Q4W administration, this Phase 3b 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 in advance of the first planned sponsor analysis when all subjects have completed Week 24 (see Section 9.2.3.1) and will not be shared with Investigators until the primary analysis at Week 48. In addition, central randomization will be used to ensure that selection bias is avoided (see Section 6.2). 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.

absorption, the recommended intake of oral CAB in the Phase 3 studies is with food at the same time as RPV.

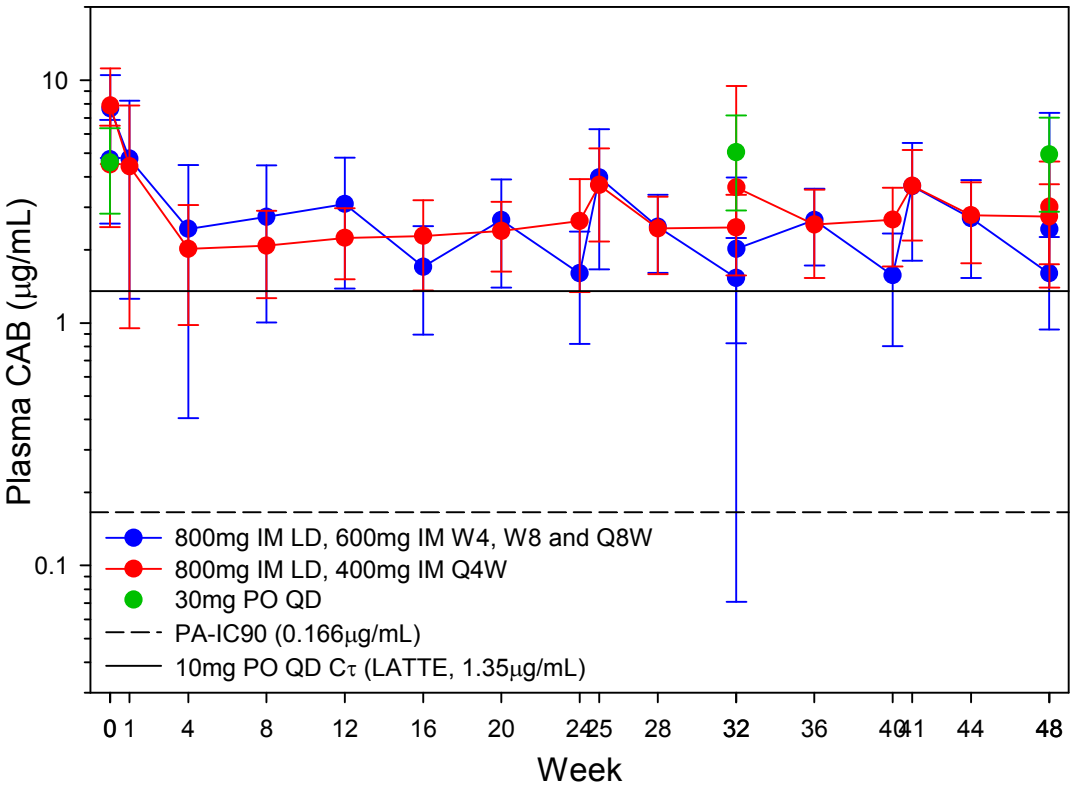
Overall, the efficacy and safety data from the LATTE study, CAB exposure following LA administration, and limited drug-drug interaction potential, support selection of the CAB 30 mg dose for once daily administration with the approved dose of RPV 25 mg once daily during the oral lead-in phase of this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

Table 3 Summary of CAB Pharmacokinetic Parameters Following Repeat Oral Administration in HIV-Infected Subjects

Study	Once Daily Dose	Phase	Plasma CAB PK Parameter (Geometric mean [95%CI] (CVb%)			
			AUC(0-τ) (μg.h/mL)	Cmax (μg/mL)	Cτ or C0 (μg/mL)	Tmax[a] (h)
LAI116482 (LATTE)	10 mg tab (n=14)	Induction Phase +2 NRTIs	45.7 [38.2, 54.6] (32)	2.77 [2.3, 3.3] (33)	1.35[b] [1.2, 1.5] (45)	1.0 (0.9 – 8.0)
		Maintenance Phase +RPV 25 mg	---	---	1.34[c] [1.1, 1.6} (58)	---
	30 mg tab (n=12)	Induction Phase +2 NRTIs	134 [110, 163] (32)	7.49 [6.3, 8.9] (28)	4.20[d] [3.8, 4.7] (40)	2.0 (1.0 – 8.0)
		Maintenance Phase +RPV 25 mg	---	---	3.93[e] [3.5, 4.4] (44)	---
	60 mg tab (2x30 mg) (n=9)	Induction Phase +2 NRTIs	195 [138, 277] (48)	11.5 [8.8, 15.0] (36)	7.93[f] [7.2, 8.8] (39)	2.0 (1.0 – 8.0)
		Maintenance Phase +RPV 25 mg	---	---	8.22[g] [7.4, 9.1] (37)	---
200056 LATTE-2 Day 1, predose	30 mg tab (n=246)	Induction Phase +2NRTIs	---	---	4.22 [4.0, 4.4} (43)]	---

a. median (range)
b. n=57
c. n=50
d. n=53
e. n=51
f. n=55
g. n=49

Figure 3 Observed Mean (SD) Concentration-Time Data following CAB LA Q8W and Q4W and Cτ following 30 mg PO QD through Week 48 (200056, LATTE-2)



Both predose and 2h post injection concentrations are shown at Time Zero, Week 32, and Week 48.

closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

7.1. Time and Events Table

Note: While some assessments included in the Time and Events Table are conducted less frequently following the primary endpoint (Week 48), IM injections for participants during the Extension Phase will continue to be administered Q4W or Q8W based on original study randomization assignment.

All patients will be randomized at Day 1 to initiate either Q4 weekly or Q8 weekly administration of IM CAB LA + RPV LA. Only participants randomized from oral SOC treatment will participate in the Day 1 to Week 4 Oral CAB + Oral RPV lead-in treatment.

7.1.1. Time and Events Table for CAB LA + RPV LA Q4 Weekly Administration

Procedure	Screening Visit [a]	Maintenance Phase																			Extension Phase		Withdrawal Assesssments [y]	Long-Term Follow-up [z]
		Week																						
		Day 1	Week 4A (Oral Lead-in ONLY)[b]	Week 4B	8	12	16	20	24	28	32	36	40	44	48	52	Q4W 56-92	Q8W 56-92	96	100	Q4W After Week 100	Q8W After Week 96		
Written informed consent	X																							
Eligibility Verification (Inclusion/Exclusion Criteria)	X		X[c]																X[c]					
Randomization		X																						
Demography	X																							
Medical History[d]	X																							
Cardiovascular risk assessment[d]	X	X																						
Medication History/ Prior ART history	X																							
Syphilis serology + Reflex Rapid Plasma Reagin (RPR)	X	X																						

Procedure	Screening Visit [a]	Maintenance Phase																			Extension Phase		Withdrawal Assessments [y]	Long-Term Follow-up [z]
		Week																						
		Day 1	Week 4A (Oral Lead-in ONLY)[b]	Week 4B	8	12	16	20	24	28	32	36	40	44	48	52	Q4W 56-92	Q8W 56-92	96	100	Q4W After Week 100	Q8W After Week 96		
Symptom Directed Physical Exam and Medical Assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, Height and BMI[f]		X													X				X				X	
Vital Signs: BP, HR, Temperature)[g]	X	X													X				X				X	
12-lead ECG [h] (triplicate at Day 1 pre-dose)	X	X													X				X				X	
CDC HIV-1 stage	X	X																						
HIV Associated Conditions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs, SAEs, Concomitant Medications[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Screening Visit [a]	Maintenance Phase																		Extension Phase	Withdrawal Assessments [y]	Long-Term Follow-up z
		Week																				
		Day 1	Week 4A (Oral lead-in ONLY) b	Week 4B (Oral lead-in ONLY) b	8	9	16	24	32	40	41	48	56	64	72	80	88	96	100	Q8W After Week 96		
Symptom Directed Physical Exam and Medical Assessment [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, Height and BMI [f]		X										X						X			X	
Vital Signs (BP, HR, Temperature) [g]	X	X										X						X			X	
12-lead ECG [h] (triplicate at Day 1 pre-dose)	X	X										X						X			X	
CDC HIV-1 stage	X	X																				
HIV Associated Conditions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs, SAEs, Concomitant Medications	X i	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISR Assessment for IM injection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

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

The eCSSRS (see Section 7.4.6) assessed at the Screening visit will assess the participant's lifetime risk (any suicidal ideation, behavior, etc. occurring over the participant's lifetime). A positive alert (indicating some risk) is not necessarily exclusionary, rather a means to assess overall risk.

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

7.2.2. Baseline Assessments

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

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

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

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

- psychiatric (e.g., depression);

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

- neurologic disorders

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

7.3. Efficacy

7.3.1. Plasma HIV-1 RNA

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

7.3.2. Lymphocyte Subsets, CD4+ and CD8+

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

7.3.3. HIV Associated Conditions

HIV-associated conditions will be recorded as per Time and Events schedule (Section 7.1). HIV-associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection (see Section 11.4).

- Injection Site Reactions (ISRs) will be assessed clinically during the Maintenance and Extension Phases for the following:

  Pain, tenderness, pruritis, warmth, bruising, discoloration, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).

- A clinical assessment (using Division of Acquired Immunodeficiency Syndrome [DAIDS] grading scale) should be performed both before and after an injection to identify resolving and new ISRs. All injection site reactions are considered adverse events. The clinical assessment and interpretation of any ISR, will be documented in the ISR AE eCRF.

- Columbia Suicide Severity Rating Scale (eC-SSRS) will be assessed as per the Time and Events Schedule (see Section 7.1 and Suicidal Risk Monitoring Section 7.4.6).

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

7.4.2. Laboratory Assessments

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

- 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 subject management or are

considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF. Local laboratory services may be used to verify pending laboratory parameters only after consultation and agreement with the study team.

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

Labs will be automatically graded by the central lab according to the DAIDS toxicity scales (See Section 11.2 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events").

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

Table 8 includes lab parameters to be assessed as per the Time and Events Schedule (see Section 7.1). 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.

Table 8 Safety Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[c]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine clearance[b]
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			
Plasma HIV-1 RNA[e]			
CD4+ and CD8+ cell counts [CD4/CD8 ratio][f]			
Peripheral Blood Mononuclear Cells (PBMCs): Day 1, Week 48, Week 96, Withdrawal only			
Hepatitis B (HBsAg), anti-HBc, anti-HBsAg, and hepatitis C antibody (Screening)[g]			
Syphilis serology + Reflex Rapid Plasma Reagin (RPR) (Screening and Baseline)			
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)			
Pregnancy test for women of childbearing potential[h]			
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate			
Genetics Sample			
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)			

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO2 = carbon dioxide, HDL = high density

lipoprotein, LDL = low density lipoprotein, HBsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [Levey, 2009].
c) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
d) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
e) For participants meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain genotype/phenotype data.
f) CD8+ cells will only be reported at Baseline, Day 1, Weeks 4b, 24, 48, and 96.
g) HBV DNA will only be performed for participants with a positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).
h) Urine pregnancy test/ serum pregnancy test will be performed according to the Time and Events Table (Section 7.1).

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

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

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- AEs will be collected from the start of Study Treatment until the final follow-up contact, at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 11.6, Appendix 6
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

7.4.3.2. Method of Detecting AEs and SAEs

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

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

7.4.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.5) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 5.5). Further information on follow-up procedures is given in Section 11.6, Appendix 6).

7.4.3.4. Prompt Reporting of Serious Adverse Events and Other Events

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to the medical monitor as described in Table 9 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 9.

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

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

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

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

- The investigator determines that the event or outcome qualifies as an SAE under part 'other situations' of the SAE definition (see Section 11.6.2), or
- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or

7.4.5.2. Diarrhea

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

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

7.4.5.3. Hypertriglyceridemia/ Hypercholesterolemia

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

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

7.4.5.4. Seizures

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

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

7.5.2. Rationale of PK Sampling Strategy

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

7.5.3. Sample Analysis

7.5.3.1. CAB Sample Analysis

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

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

7.5.3.2. RPV Sample Analysis

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

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

7.6. Genetics

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

7.7. Viral Genotyping and Phenotyping

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

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

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

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

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

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

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

7.8.3. Guidance for administering the different versions of HIVTSQc, Preference and Reason for Switch Questionnaires in ATLAS-2M

For the questionnaires not included below, HIVTSQs, HAT-QoL, ACCEPT and PIN, there only exists one version of each PRO that will be administered to all patients.

Questionnaire	Version	Week visit in ATLAS-2M	Treatment Arm in ATLAS-2M	Treatment before entering ATLAS-2M	Patients in Extension phase in ATLAS
HIVTSQc	Q4W ATLAS to Q4W ATLAS-2M	Week 48 / Withdrawal	Currently on Q4W	Randomized at Day 1 in Q4W arm in ATLAS	Even if patients remained in extension phase in ATLAS consider only the initial arm they were randomized in Day 1 in ATLAS
	Q4W ATLAS to Q8W ATLAS-2M	Week 48 / Withdrawal	Currently on Q8W	Randomized at Day 1 in Q4W arm in ATLAS	
	SOC to Q4W or Q8W ATLAS-2M	Week 48 / Withdrawal	Currently on Q4W or Q8W	Any SOC treatment: Randomized at Day 1 in SOC in ATLAS or coming outside of ATLAS	
Preference	Injection to Injection treatment	Week 48 / Withdrawal	Currently on Q8W	Randomized at Day1 in Q4W arm in ATLAS	Even if patients remained in extension phase in ATLAS consider only the initial arm they were randomized in Day 1 in ATLAS
	Oral to Injection treatment	Week 48 / Withdrawal	Currently on Q4W or Q8W	Any SOC treatment: Randomized at Day 1 in SOC in ATLAS or coming outside of ATLAS Continuing Q4W from ATLAS	

Questionnaire	Version	Week visit in ATLAS-2M	Treatment Arm in ATLAS-2M	Treatment before entering ATLAS-2M	Patients in Extension phase in ATLAS
Reason for Switch		Day 1	Currently on Q4W or Q8W	Any SOC treatment: Randomized at Day 1 in SOC in ATLAS or coming outside of ATLAS	Administer again even if patients were administered the "reason for switch" at week 52 in ATLAS.
Reason for Continuation		Day 1	Currently on Q4W or Q8W	Randomized at Day 1 in Q4W arm in ATLAS	

8. DATA MANAGEMENT

- For this study participant data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Participant initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

The study is designed to demonstrate that the antiviral effect of Q8W dosing with CAB LA + RPV LA is non-inferior to Q4W dosing CAB LA + RPV LA in subjects stably suppressed on an oral SOC regimen or Q4W CAB LA + RPV LA regimen prior to randomization. Non-inferiority in the proportion of participants with HIV-RNA ≥50 c/mL at Week 48 (defined by the US FDA snapshot algorithm) can be concluded if the upper bound of a two-sided 95% confidence interval for the difference between the two treatment arms (Q8W – Q4W) is less than 4%.

Two important changes to the current study in relation to the LATTE-2 study were also considered in setting the sample size. Firstly, the loading dose schedule for Q8W has been modified in an attempt to optimize the pharmacokinetics of CAB LA + RPV LA. Secondly, a re-testing strategy (see Section 5.5.5.1) has been added to reduce the number of subjects counted as having HIV RNA ≥ 50 c/mL in the primary analysis at key timepoints because of transient blips (consistent with the FDA's guidance for the Snapshot endpoint). Through these changes, it is possible that the proportions with HIV RNA ≥ 50 copies/mL will be lower than that observed in the LATTE-2 study.

Table 11 Snapshot Analysis Outcomes for LATTE-2 Phase IIb Study of CAB LA + RPV LA (Intent-to-Treat Maintenance Exposed Population)

Week 48			
Study	**Maintenance Treatment Arm**	**HIV-RNA <50**	**HIV-RNA ≥50**
LATTE-2 (ITT-ME) [a]	CAB LA + RPV LA Q8W (N=115)	92%	8/115 (7%)
	CAB LA + RPV LA Q4W (N=115)	91%	1/115 (<1%)
	Pooled LA (N=230)	92%	6/230 (4%)
	Oral CAB + 2NRTIs (N=56)	89%	1/56 (2%)
Week 96			
LATTE-2 (ITT-ME) [b]	CAB LA + RPV LA Q8W (N=115)	94%	5/115 (4%)
	CAB LA + RPV LA Q4W (N=115)	87%	0/115 (0%)
	Pooled LA (N=230)	90%	5/230 (2%)
	Oral CAB + 2NRTIs (N=56)	84%	5/56 (2%)

a) Participants had HIV-1 RNA <50 c/mL at Week -4 and received oral CAB 30 mg + 2 NRTIs as initial induction period therapy from Week -20 to Day 1.
b) Participants had HIV-1 RNA <50 c/mL at Week 20 and switched from oral CAB 30 mg + 2 NRTIs to Oral CAB 30 mg + RPV at Week 24.

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

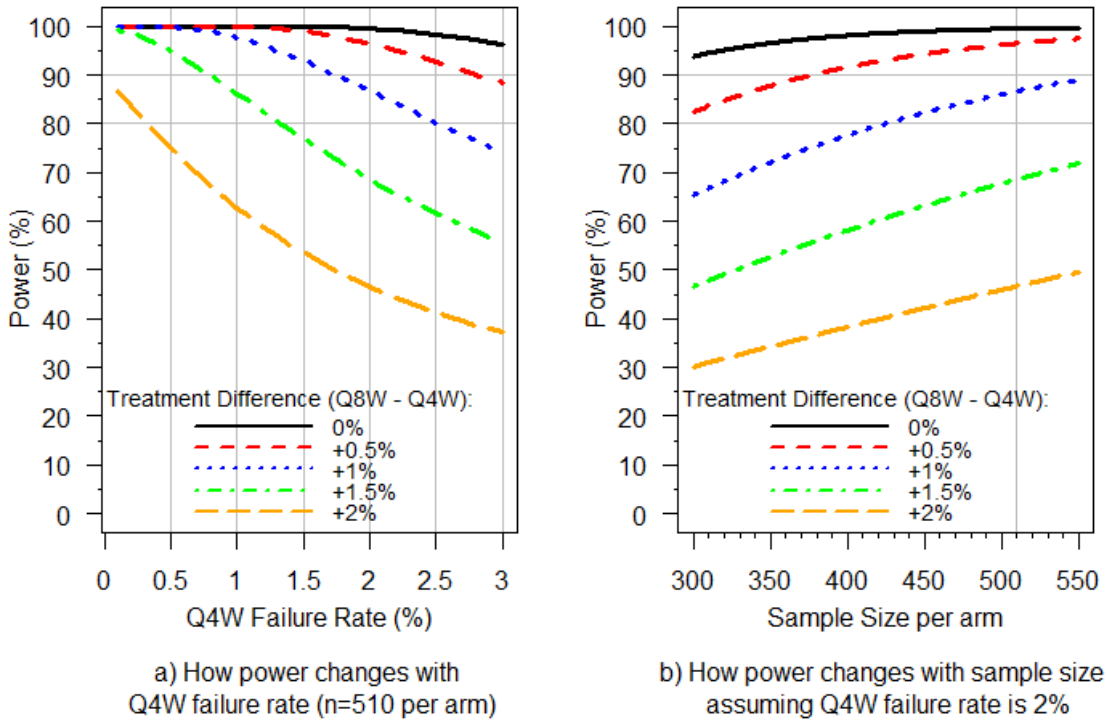
Given the response rates shown in Table 11, a reasonable assumption for the true response rate (HIV-1 RNA <50 c/mL) for both arms is 92%.

9.1.4. Sample Size Sensitivity

Figure 15a (left panel) shows the sensitivity of the power curve for the primary comparison to different assumed 'true' proportions with HIV-RNA ≥ 50c/mLwith 510 randomized participants per arm based on calculations using an unpooled Z test statistic and asymptotic approximation. For example, if the true rate for Q8W is 1.5 percentage points higher than Q4W (green line), then the study would still have over 80% power to meet its primary objective if the Q4W rate is less than 1.3%.

Figure 15b (right panel) shows the impact on power to changes in the sample size assuming a 2% true-rate for Q4W. Power remains at least 80% for sample sizes as low as 425 per arm if the true Q8W rate is at most 1-percentage point inferior to Q4W.

Figure 15 Sensitivity of Estimated Power for Snapshot Proportion with HIV-RNA ≥ 50 c/mL



a) How power changes with Q4W failure rate (n=510 per arm)

b) How power changes with sample size assuming Q4W failure rate is 2%

Figure 16a (left panel) shows the sensitivity of the estimated power for the secondary endpoint comparison of response rates (HIV-1 RNA <50 c/mL at Week 48) to different assumed 'true' response rates based on calculations using an unpooled Z test statistic and asymptotic approximation. For example, if the true Q8W rate is two percentage points inferior to Q4W (blue line), then power is at least 90% for Q4W rates greater than 82%.

Figure 16b (right panel) shows the impact on power to changes in the sample size assuming an 92% response rate for Q4W. For example, if the true Q8W rate is 3-percentage points inferior to Q4W (green line), then power remains at least 90% for sample sizes as low as 368 per arm.

with respect to change from baseline in HIVTSQs total score at Week 48 will be tested at a two-sided 5% significance level using a linear model based on the ITT-E population.

9.3.8. Genetic Analyses

See the full protocol for details about the Genetics Analysis Plan.

9.3.9. Other Analyses

Planned subgroup analyses include: proportion of participants by patient subgroup(s) (e.g., by age, gender, BMI, race, HIV-1 subtype, Baseline CD4+, type of oral treatment [NNRTI, PI, or INSTI], duration prior CAB LA and RPV LA exposure [0 weeks, 1-24 weeks, >24 weeks]) with HIV-1 RNA ≥50 c/mL, and with protocol defined confirmed virologic failure, respectively, over time including Week 48 and Week 96.

In addition, stratum-specific analyses (unadjusted treatment difference and corresponding 95% confidence interval) of the primary endpoint (proportion of participants with HIV-1 RNA ≥50 c/mL) and key secondary endpoint (proportion of participants with HIV-1 RNA <50 c/mL) at Week 48 (and Week 96) will be performed within each of the following patient populations: *(Group 1) those currently receiving Standard of Care antiretroviral therapy [no prior CAB + RPV exposure] and (Group 2) those receiving Q4W CAB LA + RPV LA therapy in the ongoing ATLAS study*). For Group 2, a stratum-adjusted analysis will also be provided, with adjustment for prior CAB + RPV exposure (1 to 24 weeks vs. >24 weeks) using Cochran-Mantel Haenszel (CMH) weights, as described in Section 9.3.1.

Changes from baseline in CD4+ lymphocyte count at Week 48 and Week 96 will also be summarized by subgroups. Additional details on subgroup analyses will be provide in the RAP.

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

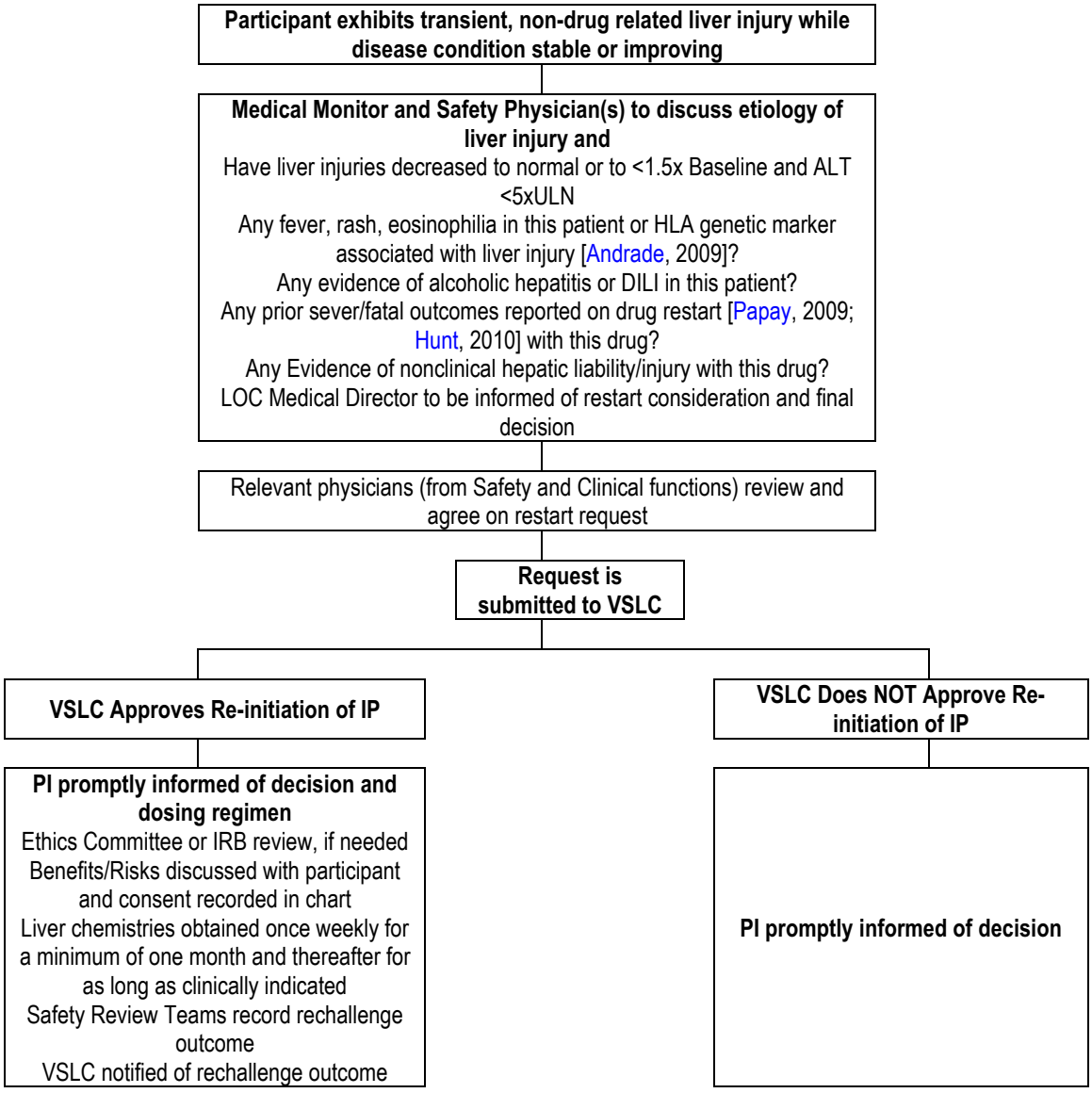
CPMS	Clinical Pharmacology Modelling and Simulation
CSR	Clinical Study Report
CV	Cardiovascular
CVF	Confirmed Virologic Failure
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DRE	Disease-Related Events
DRV	Darunavir
DTG	Dolutegravir, TIVICAY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

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.

Figure 18 VSLC process for drug restart approval or disapproval



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

11.3.4.1. 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

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.6.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc.).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen

from baseline is not considered an AE.

Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

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

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

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

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

11.6.5. Evaluating AEs and SAEs

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities • Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment. • For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Objectives	Endpoints
	Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire HIVTSQc at Week 48 (or Withdrawal). Change from Week 8 in Dimension scores ("Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time will be assessed using the Perception of iNjection questionnaire (PIN) at Weeks 8, 24, and 48 (or Withdrawal) Change from Baseline (Day 1) in treatment acceptance at Week 24 and Week 48 (or Withdrawal) will be assessed using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire

1.3. Overall Design

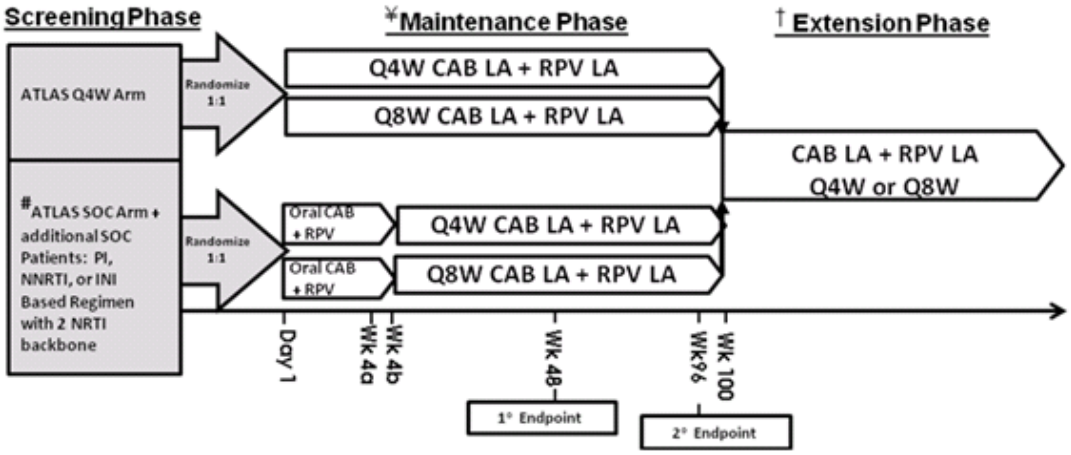
Study 207966 (**A**ntiretroviral **T**herapy as **L**ong **A**cting **S**uppression every **2 M**onths-ATLAS-2M) is a Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of CAB LA + RPV LA administered every 4 weeks compared to CAB LA + RPV LA administered every 8 weeks in approximately 1020 adult HIV-1 infected participants.

Two groups of patients who fulfill eligibility requirements will be randomized (1:1) to receive CAB LA + RPV LA Q4W, or CAB LA + RPV LA Q8W regimen for at least 100 weeks:

Group 1: Patients randomized from current ART SOC therapy

Patients randomized from current ART SOC therapy, including those enrolled to the "current ART" arm of the ATLAS study following completion of the Week 52 visit (at minimum), will begin oral therapy with CAB 30 mg + RPV 25 mg once daily at Day 1 for 28 days (±3 days) to determine individual safety and tolerability prior to receiving CAB LA + RPV LA Q4W, or CAB LA + RPV LA Q8W. For patients on SOC transitioning from the ATLAS trial, eligibility for ATLAS-2M can be determined once the final central lab results from ATLAS are available and safety parameters have been reviewed.

1.3.1. 207966 (ATLAS-2M) Study Design Schematic



N=1020, randomized 1:1 to each arm and stratified by prior CAB + RPV Exposure
# SOC Patients not transitioning from the ATLAS study must be on uninterrupted current regimen (either the initial or second cART regimen) for at least 6 months prior to Screening. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening. No history of virologic failure. No evidence of viral resistance based on the presence of any resistance-associated major INI, or NNRTI mutation (except K103N) from prior genotype assay results. No current or prior history of etravirine use.
†Optional Extension Phase to continue randomized CAB LA + RPV LA Q4W or Q8W at Wk 100
¥Participants who withdraw from IM regimen must go into 52 week long term follow up phase if randomized regimen is not yet locally approved and commercially available.

1.3.2. Number of Participants

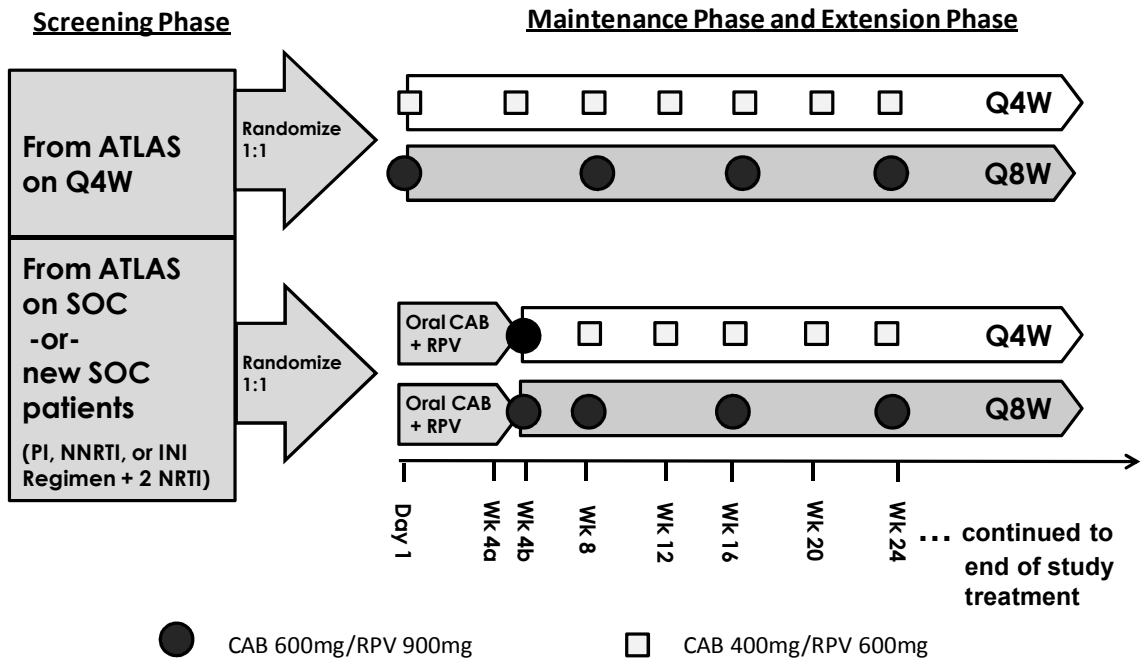
The target population to be enrolled is HIV-1 infected virologically suppressed (HIV-1 RNA <50 c/mL) patients on stable antiretroviral therapy (ART) including participants who have completed, at minimum, Week 52 of the ATLAS study.

It is anticipated that approximately 1020 participants will be enrolled into ATLAS-2M. In addition to participants rolled over from the ATLAS study, additional participants on SOC treatment will be screened to supplement enrollment such that the study can be appropriately powered. A 15% screen failure rate, for additional patients randomized from SOC treatment is anticipated. Participants will be enrolled from multiple countries which may include those countries actively participating in the ATLAS study including Australia, Argentina, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the United States.

Randomization will be stratified by prior CAB + RPV exposure: 0 weeks, 1-24 weeks, >24 weeks. A goal of this study is to enroll populations who are underrepresented in clinical studies including approximately 25% women. To provide sufficient data to determine whether either gender is correlated with treatment response, sites are expected to take into account gender in their screening strategies.

Q8W	CAB LA: Day 1 & Q8W thereafter: 600 mg	RPV LA: Day 1 & Q8W thereafter: 900 mg
All participants entering ATLAS-2M from an oral SOC regimen will receive a 4-week oral lead-in of CAB+RPV prior to receiving IM injections, except for ATLAS subjects transitioning from Q4W to Q8W injections. These participants previously established safety and tolerability of CAB + RPV within the ATLAS study.		

ATLAS-2M Treatment Schematic



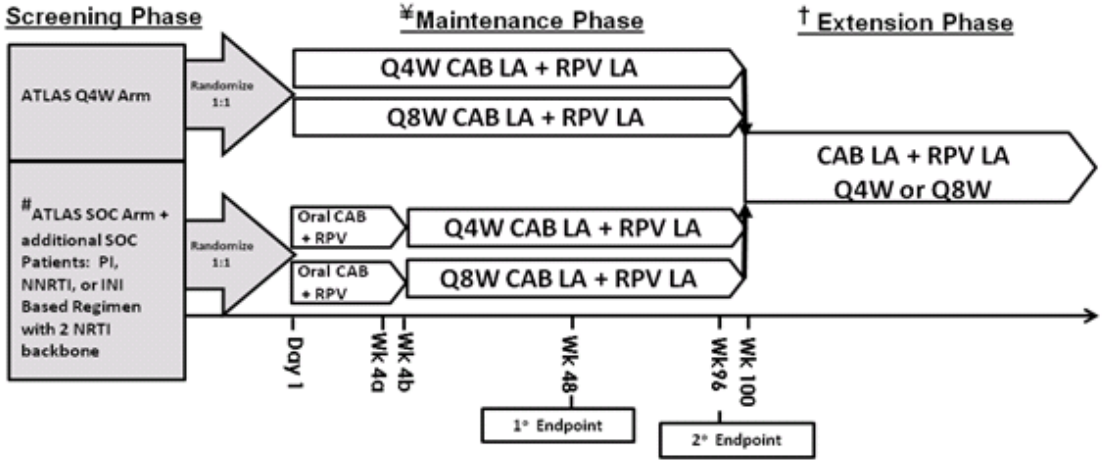
1.4.2.1. Patients randomized to LA dosing from current ART SOC therapy:

All participants randomized from current ART SOC therapy (including those transitioning from SOC in ATLAS and new study participants) will begin oral therapy with CAB 30 mg + RPV 25 mg once daily at Day 1 for 4 weeks to determine individual safety and tolerability prior to administration of CAB LA + RPV LA. The oral lead-in period is part of the Maintenance Phase and will therefore be included within the 48 and 96 week analyses.

The final dosing of current daily oral ART regimen should occur the day prior to randomization to avoid overlap of treatment regimens however, if the participant takes current ART prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1. At the Week 4a visit, safety assessments (including e.g., clinical chemistries) will be performed as per the Time and Events Table to determine individual safety and tolerability prior to the initial administration of CAB LA + RPV LA. Dosing of CAB LA + RPV LA Q4W or Q8W will initiate at the Week 4b visit once safety labs from Week 4a are available and have been reviewed.

Objectives	Endpoints
	administration over time will be assessed using the Perception of iNjection questionnaire (PIN) at Weeks 8, 24, and 48 (or Withdrawal) Change from Baseline (Day 1) in treatment acceptance at Week 24 and Week 48 (or Withdrawal) will be assessed using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire
Exploratory	
To evaluate the antiviral and immunologic effects, safety and tolerability, and viral resistance of CAB LA + RPV LA for all participants in the Extension Phase.	Proportion of participants with plasma HIV-1 RNA <50 c/mL over time Proportion of participants with confirmed virologic failure over time Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV in over time Incidence and severity of AEs and laboratory abnormalities over time Proportion of participants who discontinue treatment due to AEs over time Absolute values and changes in laboratory parameters over time Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death)
To explore the effect of patient characteristics on virologic and immunologic responses to CAB LA+ RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks	Proportion of participants by patient subgroup(s) (e.g., by age, gender, BMI, race, HIV-1 subtype, Baseline CD4+, type of oral treatment [NNRTI, PI, or INSTI], duration prior CAB LA and RPV LA exposure [0 weeks, 1-24 weeks, > 24 weeks]) with HIV-RNA greater than or equal to 50 c/mL, and with protocol-defined confirmed virologic failure over

Figure 1 207966 (ATLAS-2M) Study Design Schematic



N=1020, randomized 1:1 to each arm and stratified by prior CAB + RPV Exposure
# SOC Patients not transitioning from the ATLAS study must be on uninterrupted current regimen (either the initial or second cART regimen) for at least 6 months prior to Screening. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening. No history of virologic failure. No evidence of viral resistance based on the presence of any resistance-associated major INI, or NNRTI mutation (except K103N) from prior genotype assay results. No current or prior history of etravirine use.
†Optional Extension Phase to continue randomized CAB LA + RPV LA Q4W or Q8W at Wk 100
¥Participants who withdraw from IM regimen must go into 52 week long term follow up phase if randomized regimen is not yet locally approved and commercially available.

4.2. Treatment Groups and Duration

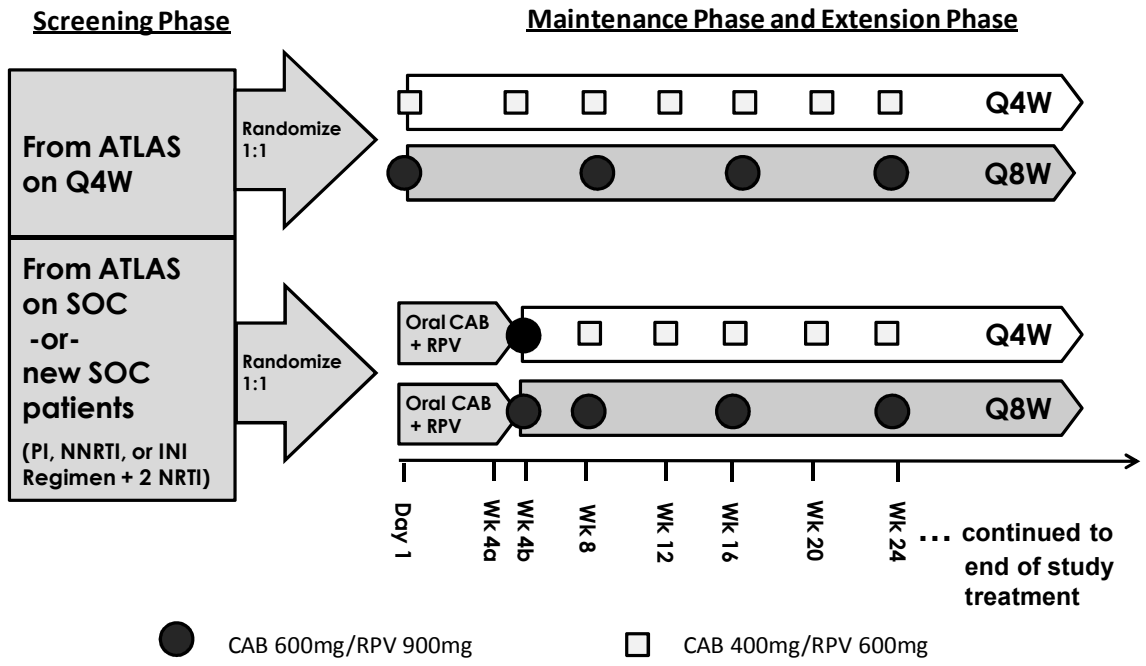
4.2.1. Screening Phase (Up to 35 days)

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

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

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

Figure 2 ATLAS-2M Treatment Schematic



4.2.2.1. Patients randomized to LA dosing from current ART SOC therapy:

All participants randomized from current ART SOC therapy (including those transitioning from SOC in ATLAS and new study participants) will begin oral therapy with CAB 30 mg + RPV 25 mg once daily at Day 1 for 4 weeks to determine individual safety and tolerability prior to administration of CAB LA + RPV LA. The oral lead-in period is part of the Maintenance Phase and will therefore be included within the 48 and 96 week analyses.

The final dosing of current daily oral ART regimen should occur the day prior to randomization to avoid overlap of treatment regimens however, if the participant takes current ART prior to coming into the clinic, randomization and initiation of oral CAB and RPV should continue as planned for Day 1. At the Week 4a visit, safety assessments (including e.g., clinical chemistries) will be performed as per the Time and Events Table to determine individual safety and tolerability prior to the initial administration of CAB LA + RPV LA. Dosing of CAB LA + RPV LA Q4W or Q8W will initiate at the Week 4b visit once safety labs from Week 4a are available and have been reviewed.

Subjects receiving oral **SOC** treatment and randomized **to Q4W** injections will receive loading doses of CAB LA 600 mg + RPV LA 900 mg on **Week 4b** followed by maintenance injections of CAB LA 400 mg + RPV LA 600 mg every 4 weeks thereafter.

Subjects receiving oral **SOC** treatment and randomized **to Q8W** injections will receive doses of CAB LA 600 mg + RPV LA 900 mg on **Week 4b and Week 8** followed by identical maintenance dose injections every 8 weeks thereafter.

4.5. Dose Justification

4.5.1. Oral Lead-In Phase

Participants entering the study from oral SOC will receive oral CAB 30 mg + RPV 25 mg once daily during the 4-week oral lead-in phase to confirm tolerability prior to receiving CAB LA + RPV LA injectable treatment. Data from study LAI116181 [GlaxoSmithKline Document Number 2011N130484_00] have demonstrated that there is no clinically relevant drug-drug interaction following repeat oral administration of CAB with RPV. Oral RPV 25 mg once daily, the approved oral dose of RPV, has been administered in combination with oral CAB to HIV-infected participants in Phase 2b studies LAI116482 [(LATTE); GlaxoSmithKline Document Number 2014N216014_00] (CAB 10, 30, or 60 mg once daily) and 200056 [LATTE-2] (CAB 30 mg, oral lead-in phase). The CAB 30mg oral dose was selected based on observed safety and efficacy from the LATTE-2 study for use during the oral lead phase of Phase 3 studies 201585 [ATLAS] and 201584 [FLAIR] which are evaluating Q4W dosing of CAB LA + RPV LA. The present study will also use CAB 30 mg once daily with RPV 25 mg once daily during the oral lead-in phase.

CAB demonstrated good short-term safety/tolerability and antiviral activity as monotherapy following oral administration of 5 mg and 30 mg once daily. LAI116482 (LATTE) is an ongoing Phase IIb, dose-ranging study (randomized 1:1:1: to CAB 10 mg, 30 mg, or 60 mg) evaluating the long-term efficacy and safety of a two-drug, two-class, once daily combination of CAB + RPV in HIV-infected, treatment-naïve adult participants. Following a 24-week phase of induction of virologic suppression using CAB + 2 NRTIs, the regimen was simplified to oral CAB + RPV once daily at Week 24 and continued for an additional 72-weeks (total comparative study duration of 96 weeks; Margolis, 2015). The results of this study also informed the Phase IIb study 200056 (LATTE-2) with intramuscular CAB LA and RPV LA.

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

4.5.2. Long Acting Injectable for Maintenance Phase

The safety and efficacy of a 2-drug regimen with CAB and RPV for maintenance of virologic suppression was established in LATTE, as detailed in Section 4.5.1, and informed the Phase 2b study (LATTE-2) with CAB LA and RPV LA. Study 200056 (LATTE-2) is an ongoing, Phase 2b dose-ranging study evaluating the long-term efficacy and safety of a two-drug, two-class combination of CAB LA + RPV LA given every 4 weeks (Q4W) or every 8 weeks (Q8W), as compared to an oral three-drug regimen, for maintenance of virologic suppression in HIV-infected, treatment-naive adults. The first phase of the LATTE-2 study was a 20-week Induction Phase (16 weeks of oral CAB + 2 NRTIs, 4 weeks of CAB + 2 NRTIs + oral RPV). Participants who were eligible to continue into the Maintenance Phase were then randomized (2:2:1) to receive IM injections of CAB LA every 4 weeks (800 mg Day 1 then 400 mg Q4W) or every 8 weeks (800 mg Day 1, 600 mg Week 4, 600 mg Week 8, then 600 mg Q8W) in combination with IM RPV LA every 4 weeks (600 mg Day 1 then 600 mg Q4W) or every 8 weeks (900 mg Day 1, 900 mg Week 8, then 900 mg Q8W), respectively, or to continue on their triple ART regimen.

The Q4W dosing strategy was selected for further investigation in Phase 3 based on observed efficacy, safety, and tolerability at Week 48. Both Q4W and Q8W regimens were continued throughout the Maintenance Phase as planned, and Week 96 results (Table 4) were supportive of further evaluation of the Q8W regimen in the present study. Moreover, LATTE-2 was amended to permit subjects to remain on their randomized LA regimen (either Q4W or Q8W) during the Extension Phase (post Week 96), and those subjects randomized to the oral comparator arm were allowed transition to either LA regimen at Week 96. Forty-four subjects 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 were administered at Week 100 following a 4-week oral lead-in where 2 NRTIs were discontinued and RPV 25 mg once daily was added to CAB 30 mg once daily.

Table 4 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)

Observed pharmacokinetic data for both CAB LA regimens in LATTE-2 are presented in Figure 3 and summarized in Table 5.

Table 5 Summary of CAB PK Parameters Following Repeat Dose Administration of CAB LA to Healthy and HIV-infected Subjects

Population	Study	CAB LA Regimen	Dosing Interval	Plasma CAB PK Parameter (Geometric mean [95%CI] (CVb%)			
				AUC(0- τ) (μg•h/mL)	Cmax (μg/mL)	Cτ (μg/mL)	Tmax[a] (day post last dose)
Healthy Subjects	LAI115428	800 mg IM/ 400 mg IM Q4W (n=10)	D1-W4	1252 [836, 1873] (61)	2.74 [1.72 4.35] (72)	1.78 [1.35, 2.36] (41)	6 (6 – 28)
			W4-W8	2010 [1619, 2494] (31)	3.79 [2.89, 4.99] (40)	2.60 [2.20, 3.07] (24)	6 (2 – 28)
			W8-W12	2182 [1798, 2647] (28)	4.03 [3.05, 5.30] (40)	2.69 [2.21, 3.27] (28)	6 (2 – 28)
			W12-W16	2473 [2063, 2965] (26)	4.41 [3.55, 5.48] (31)	3.27 [2.71, 3.94] (27)	6 (2 – 13)
HIV Infected Subjects	200056 LATTE2	800 mg IM/ 400 mg IM Q4W (n=115)	W24-W28 (n=97)	1858[b] [1719, 2007] (37)	3.50 [3.2, 3.8] (39)	2.35[c] [2.2, 2.5] (32)	6.9 (0 – 29)
			W40-W44 (n=95)	2017[d] [1847, 2203] (41)	3.50[e] [3.3, 3.8] (37)	2.56[f] [2.4, 2.7] (32)	6.9 (0 – 28)
		800 mg IM/ 600 mg IM Q8W (n=115)	W24-W32 (n=98)	3037[g] [2786, 3310] (42)	3.55 [3.2, 3.9] (56)	1.43[h] [1.3, 1.6] (54)	6.9 (0 – 59)
			W40-W48 (n=104)	3027[i] [2762, 3322] (47)	3.33 [3.1, 3.6] (47)	1.49 [1.4, 1.6] (42)	7.0 (0 – 57)

a. median (range)
b. n=84
c. n=108
d. n=80
e. n=98
f. n=86
g. n=100
h. n=93
i. n=112

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 subjects to 416 subjects 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 Q4W and Q8W LA dosing regimens for use in Phase 3 studies (Q4W) and the present study (Q4W and Q8W) as discussed in Section 4.5.2.1 and Section 4.5.2.2.

Procedure	Screening Visit [a]	Maintenance Phase																			Extension Phase		Withdrawal Assessments [y]	Long-Term Follow-up [z]
		Week																						
		Day 1	Week 4A (Oral Lead-in ONLY)[b]	Week 4B	8	12	16	20	24	28	32	36	40	44	48	52	Q4W 56-92	Q8W 56-92	96	100	Q4W After Week 100	Q8W After Week 96		
ISR Assessment for IM injections		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (eC-SSRS)[j]	X	X		X	X		X		X		X		X		X			X	X				X	
Clinical chemistry and Hematology	X	X	X	X	X		X		X		X		X		X			X	X	X		X	X	X
Pregnancy Testing[k]	S	U	S	U	S	U	S	U	S	U	S	U	S	U	S	S	U	S	S	S	U	S	S	S
HIV-1 RNA and sample for storage (S)[l]	X	X	X	X	X		X		X		X		X		X	S		X	X	S		X	X	X
CD4+ cell count	X	X		X	X		X		X		X		X		X			X	X			X	X	X
CD8+ cell count		X							X						X				X				X	
Urinalysis[m]		X	X						X						X				X				X	

Procedure	Screening Visit [a]	Maintenance Phase																		Extension Phase	Withdrawal Assessments [y]	Long-Term Follow-up z
		Week																				
		Day 1	Week 4A (Oral lead-in ONLY) b	Week 4B (Oral lead-in ONLY) b	8	9	16	24	32	40	41	48	56	64	72	80	88	96	100	Q8W After Week 96		
Columbia Suicide Severity Rating Scale (eC-SSRS) [j]	X	X		X	X		X	X	X	X		X	X	X	X	X	X	X			X	
Clinical chemistry and Hematology	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing [k]	S	U	S	U	S		S	S	S	S		S	S	S	S	S	S	S	S	S	S	S
HIV-1 RNA and sample for storage (S) [l]	X	X		X	X		X	X	X	X		X	X	X	X	X	X	X	S	X	X	X
CD4+ cell count	X	X		X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
CD8+ cell count		X						X				X						X			X	
Urinalysis [m]		X	X					X				X						X			X	
Fasting Labs Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [n]		X										X						X			X [o]	

7.4. Safety

7.4.1. Clinical Evaluations

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

- Monitoring and recording of all AEs and SAEs. Additional information on the Time Period and Frequency of Detecting AEs and SAEs is provided in Section 7.4.3.1.
- Physical exams should be conducted as part of normal routine clinical care. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).
- Height and weight will be measured and recorded. Height collected on the Day 1 (Baseline) only.
- Vital signs will include systolic and diastolic blood pressure and heart rate collected after resting for about 5 minutes. Temperature will also be collected.
- Past medical history, family history, social history, medication history. Targeted history on cardiovascular risk (smoking history, family and personal history).
- HIV-associated conditions will be recorded.
- Electrocardiogram: A 12-lead ECG will be performed in a semi-supine position after 5 minutes of rest. On Day 1 (Baseline) of the Maintenance Phase, ECGs should be performed in triplicate prior to first dose. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each participant for the site. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations. The same QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- Regular monitoring of hematology, blood chemistry, urinalysis and fasting glucose and lipids (parameters to be tested listed below).
- Periodic assessment of glucose, insulin, and bone, cardiovascular, and renal markers;
- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of CAB LA or RPV LA or as required by the Medical Monitor following a treatment interruption(s). If serum testing is required locally, the results should be available prior to the visit where urine testing is indicated per the Time and Events Schedule (Section 7.1).
- Evaluation and documentation of all concomitant medications and blood products.

Table 9 Reporting of Serious Adverse Events and Other Events

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow-up reports to be completed when the cardiovascular event or death is reported[a]	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow-up reports to be completed when the cardiovascular event or death is reported[a]	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 hours	"Pregnancy Notification Form"	Within 24 hours of investigator awareness of pregnancy outcome	"Pregnancy Follow-up Form" and SAE if required
Seizure or suspected seizure	24 hours	eCRF	24 hours	eCRF
Suspected ABC HSR in participants receiving Oral SOC during the Long-Term Follow-Up Phase[b]	1 week	ABC HSR eCRF	1 week	Updated ABC HSR eCRF
ALT≥3×ULN **and** bilirubin≥2×ULN (>35% direct) (or ALT≥3×ULN)	24 hours[c]	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable[d]	24 hours	Updated "SAE" data collection tool/"Liver Event" documents[d]
ALT≥5×ULN that persists ≥2 weeks	24 hours[c]	Liver Event eCRFd	24 hours	Updated Liver Event eCRF[d]
ALT ≥8×ULN	24 hours[c]	Liver Event eCRF[d]	24 hours	Updated Liver Event eCRF[d]
ALT ≥3×ULN (if baseline ALT is <ULN) or ALT ≥3 fold increase from baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours[c]	Liver Event eCRF[d]	24 hours	Updated Liver Event eCRF[d]

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

- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product, or

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

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

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

7.4.3.6. Regulatory Reporting Requirements for SAEs

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

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, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

7.4.3.7. Cardiovascular and Death Events

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

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

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

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

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

7.4.5.5. Creatine Phosphokinase (CPK) Elevation

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

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

7.4.5.6. Lipase Elevations and Pancreatitis

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

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

Participants with a confirmed diagnosis of clinical pancreatitis that is considered possibly or probably related to IP should have IP held. After complete resolution of the episode, participants may be re-challenged with IP after discussion with the Medical Monitor, only if the Investigator has compelling evidence that the event was not caused by IP. Upon re-challenge, lipase determinations should be performed every 2 weeks for at least 6 weeks after re-initiation of treatment. With any elevation of lipase of Grade ≥2 or any recurrence of symptoms, the participant should discontinue IP and be withdrawn from study.

7.7.1. HIV-1 Polymerase Viral Genotyping and Phenotyping

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

7.7.2. HIV-1 Exploratory Analysis

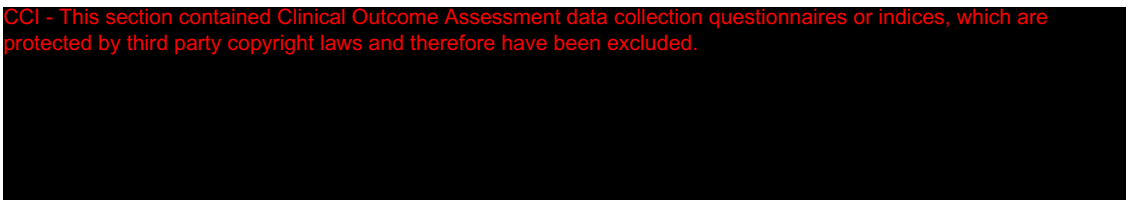
Additional analyses for HIV-1 resistance may, for example, be carried out on peripheral blood mononuclear cell (PBMC) samples collected at Baseline and/or on stored blood samples from other relevant time points. These analyses may include but are not limited to additional viral genotyping and/or phenotyping,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

7.8. Value Evidence and Outcomes

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

The "Preference" questionnaire will assess whether patients prefer the CAB LA + RPV LA injectable treatment or the daily oral ARV regimen, and assess preference for the CAB LA + RPV LA Q8W regimen or CAB LA + RPV LA Q4W regimen. The "Preference" questionnaire will include 3 questions evaluating preference of HIV treatment and the attributes supporting this preference.

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



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

7.8.1. Value Evidence and Outcomes Endpoints (Secondary)

- The "Preference" questionnaire will assess preference for CAB LA + RPV LA every 8 weeks or CAB LA + RPV LA every 4 weeks compared to oral ARV regimen, and preference for CAB LA + RPV LA every 4 weeks compared to CAB LA + RPV LA every 8 weeks at Week 48 (or Withdrawal).

- Change from Week 8 in Dimension scores (e.g., "Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of iNjection questionnaire (PIN) at Weeks 24, and 48 (or Withdrawal).

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

- Change from Baseline (Day 1) in total "treatment satisfaction" score, and individual item scores of the HIVTSQs at Weeks 24, 48 (or Withdrawal).

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

- Change from Baseline (Day1) in treatment acceptance (at Weeks 24 and 48 (or Withdrawal from the study) using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire.

- Change from Baseline (Day1) in HR QoL (using the HAT-QoL short form) at Weeks 24, and 48, (or Withdrawal).

7.8.2. Value Evidence and Outcomes Endpoints (Exploratory)

- The "Reason for Switch" question will be administered at Day 1 (Baseline) for patients randomized from oral SOC, to assess the reasons for willingness to switch ART.

- The "Reason for Switch" question will be administered at Day 1(Baseline) for patients randomized from CAB LA + RPV LA every 4 weeks in ATLAS, to assess the reasons for willingness to continue long-acting ART.

If f_{Q8W} is the snapshot failure rate for Q8W CAB LA + RPV LA, and f_{Q4W} is the snapshot failure rate for Q4W CAB LA + RPV LA then the hypotheses can be written as follows:

$$H0: f_{Q8W} - f_{Q4W} \geq 4\% \quad vsH1: f_{Q8W} - f_{Q4W} < 4\%$$

9.1. Sample Size Considerations

. This study will randomize approximately 510 participants per arm. Assuming the true proportion with HIV-1 RNA ≥50 c/mL is 3% for the Q8W arm and 2% for the Q4W arm, a non-inferiority margin of 4%, and a 2.5% one-sided significance level, this sample size would provide at least 85% power to show non-inferiority at Week 48 (using unpooled Z test statistic). With this sample size, 90% power would be achieved assuming a 1% treatment difference and true proportions with HIV-1 RNA ≥50 c/mL of 2.63% for the Q8W arm and 1.63% for the Q4W arm.

With 510 subjects per arm and assuming an observed proportion HIV-RNA ≥50 c/mL is 2% for Q4W, the largest observed treatment difference to achieve non-inferiority with respect to a 4% margin is 1.92 percentage points. This equates approximately to observing an excess of 10 subjects on the Q8W arm (10 subjects on Q4W vs. 20 subjects on Q8W).

This sample size of 510 participants per arm will also provide at least 90% power (using unpooled Z test statistic) to show non-inferiority in the proportion of participants with plasma HIV-1 RNA <50 c/mL (per FDA's snapshot algorithm) at Week 48 over a range of true response rates, on the basis of a -10% non-inferiority margin and 2.5% one-sided significance level (see Figure 15). For example, assuming true response rate for the Q8W arm and Q4W arm are both 92%, the power is ≥99% to show non-inferiority for this key secondary endpoint.

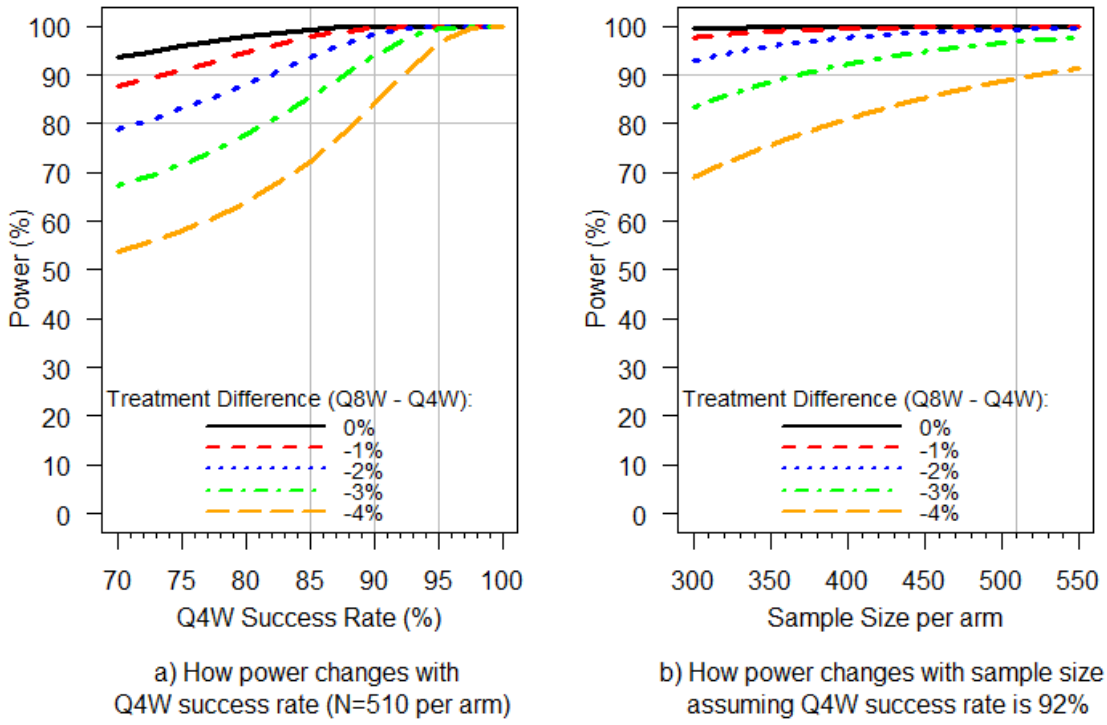
9.1.1. Rationale for non-inferiority margin

A non-inferiority margin of 4% has been chosen for this study because a snapshot proportion with HIV-1 RNA ≥50 c/mL at Week 48 in this range is considered clinically tolerable given the Q8W regimen will offer important advantages over the Q4W regimen such as reduced injection frequency, and may offer better adherence and treatment satisfaction. This margin is also in concordance with the current FDA Guidance for Industry (FDA, 2015), which is the most current regulatory guidance from either the European Medicines Agency (EMA) or FDA and includes specific recommendations regarding switch studies.

9.1.2. Assumption for Snapshot Proportion with HIV-RNA ≥50 c/mL at Week 48 (Primary Endpoint)

For the sample size calculation, assumptions regarding the true proportion with HIV RNA ≥ 50 c/mL for each arm were informed by data from the LATTE-2 Phase 2b study (Table 11). These data suggest a rate of 2% for Q4W and a possibly higher rate in the neighbourhood of 3% for Q8W.

Figure 16 Sensitivity of Estimated Power for Snapshot Proportion with HIV-RNA <50 c/mL



a) How power changes with Q4W success rate (N=510 per arm)

b) How power changes with sample size assuming Q4W success rate is 92%

9.1.5. Sample Size Re-estimation or Adjustment

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

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

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

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

9.2.1.2. Per-Protocol Population (PP)

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

10. REFERENCES

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INSTI	Integrase strand transfer inhibitor
IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IRT	Interactive response technology
ISR	Injection Site Reaction
LA	Long Acting
LDL	Low density lipoprotein
LPV	Lopinavir
LPV/r	Lopinavir-ritonavir
LTFU	Long-Term Follow-UP
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram
MSD=F	Missing, switch, or discontinuation equals failure
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRS	Numeric Rating Scale
NRTI	Nucleoside reverse transcriptase inhibitor
PI	Protease inhibitor
PIN	Perception of Injection
PK	Pharmacokinetic
PP	Per-protocol
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSRAE	Possible suicidality-related adverse event
QTc	Corrected QT interval
Q8W	Every 8 weeks
Q4W	Every 4 weeks
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RBP	Retinol Binding Protein
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RPV	Rilpivirine, Edurant
RPV LA	Rilpivirine long-acting
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
SOC	Standard of Care
SPM	Study Procedures Manual
STR	Single tablet regimen

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.

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

11.3.4.2. 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 patient must sign a new informed consent containing a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
- ***Targeted drug rechallenge or drug restart consent form must be used.***
- The patient's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed ***twice weekly for 'rechallenge' cases*** and ***once weekly for 'restart' cases*** for a minimum of one month and thereafter for as long as clinically indicated following drug re-initiation. If participant exhibits protocol-defined liver chemistry elevations, IP should be discontinued as protocol specified.
- Medical Monitor and the Ethics Committee or Institutional Review Board must be informed of the patient's outcome following drug rechallenge or restart.

Drug Rechallenge or Drug Restart Outcomes Table Template

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

Drug Rechallenge/Restart Outcomes Table – Update with each event

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

Rechallenge/restart safety outcomes:

0 = no liver chemistry elevation

1 = recurrent liver chemistry elevation not meeting participant stopping criteria

2 = recurrent liver chemistry elevation meeting participant stopping criteria

3 = serious adverse event

4 = fatality

11.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

11.6.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the eCRF • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records prior to submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Participant-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. • The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

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

11.6.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.