TITLE PAGE

Protocol Title: A Phase IIb, Multicenter, Open-label, Rollover Study Evaluating the Efficacy, Safety and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Administered Every Two Months in HIV-1 infected Adults who are Virologically Suppressed and Participated in Study LAI116482

Protocol Number: 209035/02

Compound Number: GSK1265744

Study Phase: Phase 2b

Short Title: Phase 2b, open-label, multicenter, rollover study to assess antiviral activity and safety of CAB LA + RPV LA, administered every 2 months, in HIV positive participants from the LATTE study.

Sponsor Name and Legal Registered Address:

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

US IND Sponsor Legal Registered Address:

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Sponsor Legal Registered Address (excluding US):

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

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s):

IND: 109, 678

EudraCT: 2017-002946-62

Approval Date: 19-MAY-2020

SPONSOR SIGNATORY:

PPD

MAY 19, 2020

Kimberly Smith , MD
SVP and Head, Research & Development
Chief Scientific Officer
ViiV Healthcare

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	19-May-2020	2018N356280_02
Amendment 1	22-Jun-2018	2018N356280_01
Original Protocol	16-May-2018	2018N356280_00

Amendment 2, 19-MAY-2020

Overall Rationale for the Amendment: This amendment is to include information on COVID-19 specific guidance for clinical trial continuity (participant and study management) during the pandemic.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 6.7 Dose Modifications Section 6.7.1.1. Oral Bridging Section 8.5. Adverse Events and Serious Adverse Events Section 9 Data Management	Added reference to COVID-19 Section 12.10, Appendix 10	To link Appendix 10 to the main body of the protocol
Section 12.10 Appendix 10: COVID-19 Pandemic and Clinical Trial Continuity	Added Appendix 10	To summarize COVID-19 related patient management updates that were previously communicated in a memo to investigators

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase IIb, Multicenter, Open-label, Rollover Study Evaluating the Efficacy, Safety and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Administered Every Two Months in HIV-1 infected Adults who are Virologically Suppressed and Participated in Study LAI116482

Short Title: Phase 2b, open-label, multicenter, rollover study to assess antiviral activity and safety of CAB LA + RPV LA, administered every 2 months, in HIV positive participants from the LATTE study.

Rationale:

While advances in the development of new anti-retroviral therapies (ART) provide extensive insights into the management of HIV-infected individuals, chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with the long-term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. There is an enduring need to develop new agents with improved safety and resistance profiles with convenient dosing for both antiretroviral treatment-naive and treatment-experienced participants.

This clinical trial, 209035 (Oral (**PO**) to Long Acting (**LA**) **R**ollover-POLAR), will evaluate an antiretroviral treatment approach that is potentially more convenient for the participant. Participants will rollover from the LAI116482 (LATTE) study with demonstrated HIV-1 ribonucleic acid (RNA) suppression while receiving a two-drug regimen consisting of once-daily oral CAB 30 mg + RPV 25 mg. The participants will be offered the option to switch to the LA formulations of the regimen consisting of CAB LA + RPV LA for the continued maintenance of HIV-1 RNA suppression, being dosed by intramuscular injection every 2 months (Q2M) or the oral fixed dose combination (FDC) of DTG + RPV for the continued maintenance of HIV-1 RNA suppression.

Those entering this study who do not wish to receive injectable CAB LA + RPV LA are eligible to elect to transition to once-daily oral therapy with a single tablet regimen (STR) of DTG + RPV for a period of at least 12 months, or until commercial availability. The efficacy of DTG + RPV, or Juluca, is supported by data from 2 open label, controlled trials (SWORD-1 and SWORD-2) in virologically suppressed participants switching from their current antiretroviral regimen.

The overall objective of this study is to demonstrate the antiviral activity of CAB LA + RPV LA every 2 months in virally-suppressed HIV-1 infected antiretroviral therapy ART-experienced participants. An evaluation of the antiviral activity, tolerability, durability and safety of the IM dosing regimen will be performed.

This study consists of a Maintenance Period and a Long-Term Follow Up Period for participants who withdraw and have received at least one dose of CAB LA and / or RPV LA.

Objectives and Endpoints:

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

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

Overall Design:

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

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

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

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

Participants in POLAR who successfully complete Week 300 in the LATTE study (without meeting study defined withdrawal criteria) will be given the option to receive either CAB LA + RPV LA (administered Q2M) or oral DTG + RPV daily until study intervention is either locally approved and commercially available within the local sector (including through local public/government health sectors), the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA + RPV LA Q2M is terminated.

Any participant who receives at least one dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason will enter a 52-week Long-Term Follow-Up (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.

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

Disclosure Statement:

This is an Intervention Model (Parallel) Primary Purpose (Treatment) study with Number Arms (2) No masking.

Number of Participants:

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

Intervention Groups and Duration:

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

All participants with an undetectable HIV-1 RNA (<50 c/mL) at Week 300 in the LATTE study are eligible to enter this study. A single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor. Participants with HIV-1

RNA ≥200 c/mL at Week 300 are not eligible to enter the study and will not be allowed a repeat to determine eligibility. The Day 1 visit of the POLAR study will be performed in parallel with the final closeout visit for the LATTE study, Week 312 or (if contracts have not been finalized and/or institutional review board (IRB) approval has not been obtained by Week 312 in the LATTE study) Week 324.

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

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

In addition to the viral load criteria above, if in the opinion of the Investigator, a participant experiences a significant safety event while taking either CAB or RPV, study eligibility will be determined ONLY in consultation with the medical monitor.

Participants ineligible for this study will be withdrawn from LATTE.

Maintenance Phase (Day 1 up to Commercial Approval)

At the Day 1 visit (the start of the first month of the study), participants will return to the clinic, take the last dose of their oral (CAB 30 mg + RPV 25 mg), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). The second loading injections will be administered 1 month (Month 2 visit, the start of the second month of the study) after initial loading dose (CAB LA 600 mg + RPV LA 900 mg), with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring every 2 months thereafter. The dosing window for the second injection will be -7 days from the projected dosing visit.

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

Participants will continue CAB LA + RPV LA until:

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

Safety and efficacy assessments will be conducted as per the Time and Events schedule. Dosing will occur according to the selected regimen.

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

Participants electing to receive oral DTG + RPV once daily

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

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

Safety and efficacy assessments will be conducted as per the Time and Events schedule. Dosing will occur according to the selected regimen.

LTFU Phase – IM Regimen Only

Any participant who receives at least one dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. **Investigators must discuss the choice of the follow-up HAART regimen with the Medical Monitor prior to initiating the new regimen with the participant. HAART therapy should be initiated within 8 weeks after the last Q2M injection, however if withdrawn due to virologic failure, HAART should be initiated as soon as virologic failure is confirmed. Discuss with medical monitor.** The LTFU will begin the day of the last CAB LA and/or RPV LA dose and continue for 52 weeks. These participants will not complete a Withdrawal visit, but will instead move directly into the LTFU as per the Time and Events Schedule. In addition, for participants who withdraw during the LTFU, the final visit will be considered the study withdrawal visit.

Participants will be assessed with clinic visits at months 1, 3, 6, 9, and 12 during the LTFU Phase. Female participants of child bearing potential must continue to use adequate contraception methods for the entire year of follow up.

In order to assure that participants have access to HAART during the LTFU, ViiV Healthcare may supply HAART regionally or reimbursement will be provided as needed during this phase. The LTFU Phase may be shortened or terminated at any time during

the study for various reasons, e.g., better understanding of risks of development of resistance as CAB and RPV exposures decline, end of study timings, etc.

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

Dose Modifications

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

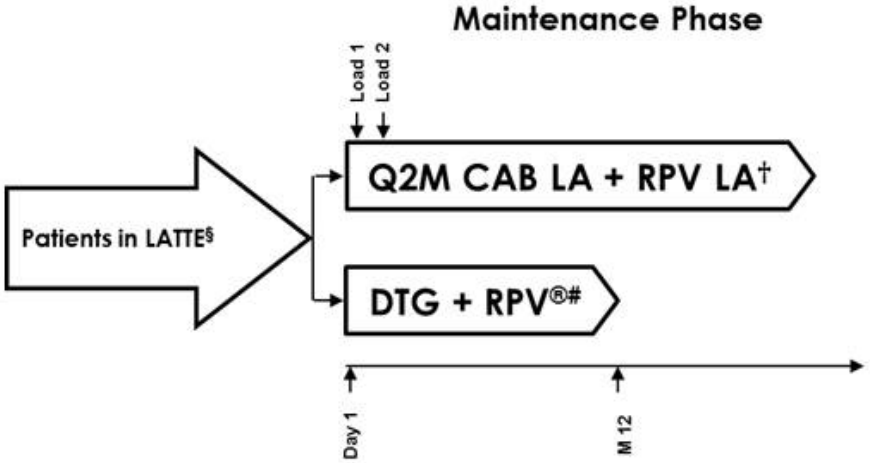
In exceptional circumstances, and in consultation with the Medical Monitor, Investigators may provide oral CAB and/or RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. Should a participant need "oral bridging", sites must contact the Medical Monitor for guidance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

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

Data Monitoring Committee: No

1.2. Schema

209035 (POLAR) Study Design Schematic



§ All participants in LATTE administered oral CAB 30 mg + RPV 25 mg

† Access commercially once Q8W is approved
# Access longer term via commercial route. Participants will continue to receive DTG + RPV if located in a region where not commercially available.

Participants transitioning from the LATTE study on oral CAB + RPV treatment will transition to their elected treatment regimen, either Q2M administration of CAB LA + RPV LA or oral DTG + RPV single tablet regimen. Regardless of treatment arm, the investigator should instruct all participants on the importance of treatment adherence. This study has an open-label design. Dosing is outlined below.

Dosage and Administration

Maintenance Phase (Day 1 to End of Study+)	
Q2M Arm- Transitioning from LATTE	
First Injections (Loading Doses) – Day 1 and Month 2	
Day 1	• Receive last dose of oral CAB + RPV regimen • Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Month 2	• Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Maintenance Injections – every 2 months (Q2M) following Month 2	
Month 4 to End of Study+ (two 3 mL injections every 2 months)	• Receive CAB LA 600 mg given as 1 X **3** mL IM injection • Receive RPV LA 900 mg given as 1 X **3** mL IM injection
Oral DTG + RPV Arm – Transitioning from LATTE	
Day 1 to Month 12 (once daily FDC tablet taken with food)	• Take one tablet of DTG 50 mg + RPV 25 mg once daily
+Until locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of CAB LA or RPV LA is terminated	

1.3. Schedule of Activities (SoA)

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

Procedures Q2M	Day 1 [a]	Month													WD [l, m]
		2 [o]	4	6	8	10	12	14	16	18	20[b]	22[b]	24	26	
Written Informed Consent	X														
Demography	X														
Eligibility Verification	X														
Physical Exam	X														
Medical History	X														
Center for Disease Control and Prevention (CDC) Classification	X														
Rapid Plasma Reagin (RPR)	X														
Symptom Directed Physical Exam, injection site reaction (ISR) and Medical Assessment [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (blood pressure [BP], heart rate [HR]) [d]	X	X	X		X		X		X		X		X		X

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

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

Procedures Q2M	**Day 1 [a]**	**Month**												**WD [l, m]**
		2 [o]	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20[b]**	**22[b]**	**24**	**26**	
Participant Visit Reminder Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant Contact Detail Confirmation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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

a. The Day 1 visit will take place during Week 312 (or Week 324 in the event of unavoidable delays) of the LATTE study, the participant's last week on study. LATTE participants eligible for POLAR study dosing will take final dose of CAB 30 mg + RPV 25 mg in the clinic within 2 hours of the Q2M IM regimen. For IM dosing administration loading doses are required. (Day 1=1st loading dose; Month 2=2nd loading dose)
b. Continue this pattern for visits for the remainder of the study. For example, Month 28 will be conducted just like Month 20, Month 30 will be conducted just like Month 22 and so on.
c. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the electronic case report form (eCRF). Medical assessments include any decisions the study staff must make for participant management.
d. Measure vital signs after about 5 minutes of rest in a semi-supine position.
e. Height collected at Day 1 only.
f. On Day 1, ECGs should be performed in triplicate at least 5 minutes apart and following 5 minutes of rest in a semi-supine position within 1 hour prior to first dose. Also on Day 1, a 2-hour post dose ECG will be performed for all participants. The 2-hour post dose ECG on Day 1 can also be used for the LATTE Week 312 (or Week 324, if needed) visit. ECG evaluations at other visits should be obtained after dosing, preferably 2-4 hours post dosing.
g. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), participant will need to be withdrawn.
h. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures.
i. Fast overnight; however, a minimum of a 6 hour fast is acceptable.
j. Take PK samples pre-dose.
k. Q2M Injections are 1 x CAB LA 600 mg IM + 1 x RPV LA 900 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the month in which the participant's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window from date of projected visit is stipulated for IM dosing. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**

l. Or Long-Term Follow Up
m. Follow Up Visit - Conduct ~4 weeks after the last dose of investigational product (IP) if not entering Long-Term Follow Up and only if the participant has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.

Time and Events Table for DTG + RPV Administration

Procedures for DTG+RPV	Day 1 [a]	Month 3	Month 6	Month 9	Month 12	WD [j]	Notes
Written Informed Consent	X						a. The Day 1 visit will take place during Week 312 (or Week 324 in the event of unavoidable delays) of the LATTE study, the participant's last week on study. LATTE participants eligible for POLAR study dosing will take final dose of CAB 30 mg + RPV 25 mg in the clinic. See Section 6.2 for dosing administration. b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for participant management. c. Measure vital signs after about 5 minutes of rest in a semi-supine position. d. Height collected at Day 1 only. e. On Day 1, ECGs should be performed in triplicate at least 5 minutes apart and following 5 minutes of rest in a semi-supine position within 1 hour prior to first dose. Also on Day 1, a 2-hour post dose ECG will be performed for all participants. The 2-hour post dose ECG on Day 1 can also be used for the LATTE Week 312 (or Week 324, if needed) visit. ECG evaluations at other visits should be obtained after dosing, preferably 2-4 hours post dosing. f. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures. g. A (-) urine pregnancy test is required prior to any administration of drug and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), participant will need to be WD.
Demography	X						
Eligibility Verification	X						
Physical Exam	X						
Medical History	X						
CDC Classification	X						
RPR	X						
Symptom Directed Physical Exam and Medical Assessment [b]		X	X	X	X	X	
Vital Signs(BP, HR) [c]	X	X	X	X	X	X	
Weight, Height & BMI [d]	X	X	X	X	X	X	
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X	

Procedures for DTG+RPV	Day 1 [a]	Month 3	Month 6	Month 9	Month 12	WD [j]	Notes
12-Lead ECG [e]	X				X	X	h. Fast overnight; however, a minimum of a 6 hour fast is acceptable. i. DTG 50 mg + RPV 25 mg. Administer daily with food j. Follow Up Visit - Conduct ~4 weeks after the last dose of IP and only if the participant has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.
HIV-1 RNA	X	X	X	X	X	X	
CD4+	X	X	X	X	X	X	
Plasma for Storage [f]	X	X	X	X	X	X	
PK Sample for Storage						S	
Clinical Chemistry and Hematology	X	X	X	X	X	X	
Pregnancy Testing [g]	U	U	U	U	U	U	
Urinalysis	X					X	
Fasting: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides [h]	X					X	
PT/PTT/INR	X					X	
HIVTSQc					X	X	
HIVTSQs	X		X		X	X	
HIVDQoL	X		X		X	X	
Participant Visit Reminder Contact	X	X	X	X	X		
Participant Contact Detail Confirmation	X	X	X	X	X		

Procedures for DTG+RPV	Day 1 [a]	Month 3	Month 6	Month 9	Month 12	WD [j]	Notes
Study Treatment Dispensation [i]	X	X	X	X	X		

Time and Events Table for Long Term Follow Up

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

Procedures for Long-Term Follow Up	Month 1 [a]	Month 3	Month 6	Month 9	Month 12	WD	Notes
Contraception Counselling [d]	X	X	X	X	X	X	
HAART Dispensation [e]	X	X	X	X	X	X	

2. INTRODUCTION

2.1. Study Rationale

While advances in the development of new anti-retroviral therapies (ART) provide extensive insights into the management of human immunodeficiency virus (HIV)-infected individuals, chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with the long-term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. There is an enduring need to develop new agents with improved safety and resistance profiles with convenient dosing for both antiretroviral treatment-naive and treatment-experienced participants.

This clinical trial, 209035 (Oral (**PO**) to Long Acting (**LA**) **R**ollover-POLAR), will evaluate an antiretroviral treatment approach that may be more convenient for the participant (see Section 4.1 for study schematic). Participants will rollover from the LAI116482 (LATTE) study with demonstrated HIV-1 ribonucleic acid (RNA) suppression while receiving a two-drug regimen consisting of once-daily oral cabotegravir (CAB) 30 mg + rilpivirine (RPV) 25 mg. The participants will be offered the option to switch to the LA intramuscular injections of CAB LA + RPV LA every 2 months (Q2M) or the oral fixed dose combination (FDC) of dolutegravir (DTG) + RPV for the continued maintenance of HIV-1 RNA suppression.

Those entering this study who do not wish to receive injectable CAB LA + RPV LA are eligible to elect to transition to once-daily oral therapy with a single tablet regimen of DTG + RPV for a period of at least 12 months, or until commercial availability. The efficacy of DTG + RPV, or Juluca, is supported by data from 2 open label, controlled trials (GlaxoSmithKline Document Number 2016N287382_03 [SWORD-1] and GlaxoSmithKline Document Number 2016N287539_02 [SWORD-2]) in virologically suppressed participants switching from their current antiretroviral regimen.

The overall objective of this study is to demonstrate the antiviral activity of CAB LA + RPV LA every 2 months in virally-suppressed HIV-1 infected antiretroviral therapy ART-experienced participants. An evaluation of the antiviral activity, tolerability, durability and safety of the intramuscular (IM) dosing regimen will be performed.

This study consists of a Maintenance Period and a Long-Term Follow Up Period for participants who withdraw and have received at least one dose of CAB LA and / or RPV LA.

2.2. Background

It is estimated that 36.7 million people are currently living with HIV/Acquired Immunodeficiency Syndrome (AIDS) and that the worldwide epidemic continues to grow at a rate of two million new infections and cause 1.1 million deaths per year [UNAIDS, 2016]. Chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues

associated with long term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires a need for continuous improvement on the durability, tolerability and convenience of all antiretroviral classes.

One approach is simplifying from an oral 3-drug regimen to a long-acting 2-drug injectable regimen. The 200056 study (GlaxoSmithKline Document Number 2013N168152_09, Study [LATTE-2]) is an ongoing Phase 2b study designed to assess the induction of virologic suppression with CAB 30 mg daily + two NRTIs, followed by a maintenance period where participants are randomized (1:2:2) to continue on oral CAB 30 mg + two nucleoside reverse transcriptase inhibitor (NRTIs) or switch to an IM injection of CAB LA + RPV LA administered every 4 weeks (Q4W) or once every 8 weeks (Q8W). A total of 309 participants were enrolled and treated.

During the Induction Phase, there was a rapid and sustained decline in HIV-1 RNA, with 91% of participants (282/309) achieving HIV-1 RNA <50 c/mL through 20 weeks of therapy. There was a single participant (with known compliance issues) with confirmed virologic failure during the Induction period. Virologic testing revealed no treatment emergent phenotypic or genotypic resistance in this participant.

The primary endpoint for 200056 was the Week 32 proportion of participants with HIV-1 RNA <50 c/mL (Snapshot, Intent-to-Treat Maintenance Exposed population [ITT-ME]). Following virologic suppression on three drug oral therapy in the Induction Phase, 286 participants qualified to enter randomization at the Day 1 visit, and were subsequently randomized 2:2:1 onto once Q4W IM injections with CAB LA + RPV LA Q4W, Q8W IM injections with CAB LA + RPV LA or continuation of oral CAB + NRTIs, respectively. Through 32 weeks of two-drug maintenance therapy, 95% (Q8W) and 94% (Q4W) of participants on injectable dosing were virologic successes, compared to 91% of participants continuing three drug oral CAB + NRTIs, meeting pre-specified criteria for comparability between the dosing arms.

At Week 96, 94% (Q8W IM) and 87% (Q4W) of participants receiving injectable dosing maintained virologic suppression (HIV-1 RNA <50 c/mL) compared to 84% of participants receiving oral CAB plus ABC/ lamivudine (3TC). Of the participants receiving Q8W IM dosing, 4% failed snapshot for virologic reasons (n=2, HIV-1 RNA >50 c/mL; n=1, lack of efficacy; n=2, withdrawal for other reasons with HIV-1 RNA >50 c/mL). No participants on Q4W IM dosing failed snapshot due to virologic reasons. There were 2 protocol-defined virologic failure (PDVFs) on Q8W dosing, and 1 PDVF on the oral dosing arm, with evolution of resistance (treatment-emergent reverse transcriptase mutations K103N, E138G, and K238T; integrase mutation Q148R). A good response was observed across all arms with no significant differences between arms with regard to increases in mean Cluster of Differentiation 4 (CD4+) cell count from Baseline.

CAB LA + RPV LA was well tolerated through Week 96 for both the Q8W and Q4W dosing regimens, as demonstrated by a low discontinuation rate due to adverse events (AEs), including injection site reaction (ISR) related AEs in either dosing arm, with no significant dose-dependent trends in safety parameters. Through Week 96, the proportion of AEs leading to withdrawal during the study Maintenance Period was low across all

arms (Q8W IM: n=2, 2%; Q4W IM: n=8, 7%; Oral CAB; n=1, 2%), with only one additional AE leading to withdrawal since the Week 48 analysis.

Long-acting two class therapy consisting of CAB LA + RPV LA as an IM regimen has the benefit of being a NRTI-sparing regimen for long-term treatment of HIV infection which will avoid known NRTI-associated adverse drug reactions and long-term toxicities. Additionally, a two-drug combination therapy with CAB LA plus RPV LA may offer a better tolerability and resistance profile, as well as improved adherence and treatment satisfaction in virologically suppressed participants improving the quality of life for participants with living with HIV. Two Phase 3 studies FLAIR and ATLAS are currently ongoing.

2.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with oral and CAB LA or RPV LA can be found in the Investigator's Brochures (2017 CAB IB: GlaxoSmithKline Document Number RH2009/00003/07; RPV IB, 2017).

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

2.3.1. Risk Assessment

Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)

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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug Induced Liver Injury (DILI)	A small proportion of participants in the CAB program to date (total exposure approximately 2376 to 17 Dec 2017) have developed transaminitis (elevated liver transaminases characterised by predominant alanine aminotransferase (ALT) elevation). In most participants, transient transaminitis was explained by acute hepatitis C infection (majority) and other systemic infections. In a small number of participants, there was not an alternative explanation, suggesting a mild form of drug induced liver injury (DILI) without hepatic dysfunction, which resolved upon withdrawal of treatment with CAB. All four participants with suspected DILI identified in Phase 2 HIV treatment studies, were receiving oral CAB.	• Exclusion criteria as described in Section 5.2 will prohibit participants with significant liver impairment based on screening liver chemistry including transaminases (ALT and Aspartate aminotransferase [AST]) as well on prior medical history. Participants with a history of chronic liver disease with ongoing inflammation and/or fibrosis will have additional confirmatory assessments to confirm suitability for entry into the study. • Liver transaminases (ALT and AST) will be monitored throughout this study (refer to Time & Events Table) and the liver chemistry stopping criteria will be adopted as described in Section 7.1.1.1 of this protocol. Participants will be withdrawn from CAB treatment where no compelling alternative cause is identified and DILI is suspected. • Participants who develop ALT ≥5 times the upper limit of normal (ULN) while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA + RPV LA.
Injection Site Reactions (ISRs)	Clinical, experience to date has demonstrated ISRs occur in the majority of exposed participants treated with CAB LA but are generally mild (Grade 1) or moderate (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days duration (median duration for individual events <1 week). ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well tolerated and have not to date been associated with an excess of	• Administration advice will be given to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and treatment of ISRs is given in study documentation • Advice will be given to participants on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	participants' withdrawal. None of the ISRs reported to date have been serious.	• Participants will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. • Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored • Significant ISRs may be photographed and referred to a dermatologist for specialist advice.
Hypersensitivity Reactions (HSR)	Hypersensitivity reactions have been reported as uncommon occurrences with integrase inhibitors (INI), including the closely related compound dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. While there have been no clinical cases of hypersensitivity to CAB to date, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic symptoms associated with use of IM CAB. The long exposures anticipated after IM CAB injection may complicate the management of a drug hypersensitivity reaction, were it to occur.	• The risk of developing a hypersensitivity reaction post administration of IM CAB is minimized since the participants in this study have been administered oral CAB 30 mg + oral RPV 25 mg within the LATTE study for at least 192 weeks. • Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study (refer to Time & Events Table, Section 8.1). Results from these assessments may aid early detection of HSR. • Participants receiving the injection would not receive further injections. During oral (oral bridge) and IM CAB

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		treatment, any HSR reactions that occur would be managed supportively.
Effects in late stage pregnancy seen in non-clinical studies	Non-clinical data from rat pre- and postnatal (PPN) studies have indicated reduced survival and viability rates amongst rat pups during the first 4 days of life at the maximum tested dose of 1000 mg/kg/day (maternal exposure). no-observed-adverse-effect-level (NOAEL) was established at the mid dose 5 mg/kg/day, the maternal exposure at this dose calculated using systemic exposure from non-pregnant rats is >20 fold predicted maximum concentration (Cmax) and area under curve (AUC) exposures for anticipated clinical CAB LA exposures for HIV treatment The clinical significance in humans of these findings is unknown.	• As a routine precaution, pregnant women are excluded from participation in this study at this time and females of reproductive potential (FRP) are required to adopt highly reliable means of contraception during participation and throughout the long term follow up phase of this study following exposure to CAB LA. • FRP are also required to undergo regular pregnancy testing throughout study conduct to enable early discontinuation of CAB LA once pregnancy is identified.
Development of Resistance following discontinuation of CAB LA	Residual concentrations of CAB would remain in the systemic circulation of participants who stop CAB LA treatment for prolonged periods (more than 1 year, in some participants, GlaxoSmithKline Document Number 2016N269422_00) after last injection (e.g., for tolerability issues or treatment failure). Participants discontinuing CAB LA regimen may be at risk for developing HIV-1 resistance to CAB many weeks after discontinuing injectable therapy.	• After participants stop CAB LA, Oral highly active antiretroviral therapy (HAART) regimens will be prescribed within 8 weeks after the last Q2M dose, and following consultation with the medical monitor. This would be anticipated to result in continued suppression or rapid resuppression of HIV-1 RNA thus minimizing the risk of emergent resistance • The participants in this study who discontinue IM CAB for any reason will be monitored for a minimum of 52 weeks from the time of the last IM CAB injection.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for CAB and CAB LA, refer to Section 6.11 CAB and CAB LA should not be co-administered with the following medicinal products, as significant decreases in CAB plasma concentrations may occur (due to UDP-glucuronosyltransferase (UGT) enzyme induction), which may result in loss of therapeutic effect of CAB. - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin - the antimycobacterials rifampicin, rifapentine, rifabutin - St John's wort (Hypericum perforatum) Oral CAB administration only: Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB. Participants discontinuing a LA regimen may be at risk for developing drug-drug interactions (DDIs) many weeks after discontinuing injectable therapy.	• All participants will be informed of prohibited medications throughout the study and updates provided as needed via the informed consent.
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that CAB LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher than expected concentrations of CAB shortly after injection and lower concentrations thereafter. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of overdose with CAB LA are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.	• Training will be provided to all sites on proper injection technique. • Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose electrocardiogram (ECG), vital signs, or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor will be notified.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all participants. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints for determination of CAB concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB concentrations.

ORAL RPV

For safety and risk mitigation for oral RPV refer to the RPV local prescribing information [Edurant Prescribing Information, 2018].

RPV LA

Information about the clinical experience to date and possible risks associated with treatment using RPV LA can be found in the Summary of Data and Guidance for the Investigator section of the IB. Beyond what has already been identified with oral RPV, no new systemic adverse reactions to RPV LA (same active moiety) have been observed. The following risks are considered to be of specific clinical relevance in the context of IM use.

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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		medical intervention, including referral to dermatologist as appropriate, should be instituted for these events; daily follow-up is recommended for 5 days from the onset of the event to monitor for progression of the event. See Section 8.7.12 for additional guidance on management of rash events.
Development of Resistance	Residual concentrations of RPV LA can remain in the systemic circulation of participants who stopped treatment (e.g., for tolerability issues or treatment failure) for prolonged periods (months to more than a year, in some participants, McGowan, 2016). Participants discontinuing a LA regimen may be at risk for developing resistance to RPV many weeks after discontinuing injectable therapy.	• After participants stop RPV LA, Oral HAART regimens will be prescribed within 8 weeks after the last Q2M dose, and following consultation with the medical monitor. This would be anticipated to result in rapid resuppression of HIV-1 RNA thus minimizing the risk of emergent resistance • The Sponsor will continue to monitor participants in this study who discontinue a LA regimen for any reason for a minimum of 52 weeks from the time of the last LA administration.
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for RPV and RPV LA, refer to Section 6.11 RPV LA should not be co-administered with the following medicinal products, as significant decreases in RPV plasma concentrations may occur (due to CYP3A enzyme induction), which may result in loss of therapeutic effect of RPV LA. - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin - the antimycobacterials rifampicin, rifapentine, rifabutin	• All participants will be informed of prohibited medications throughout the study and updates provided as needed via informed consent.

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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that RPV LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher than expected concentrations of RPV shortly after injection and lower concentrations thereafter. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. In addition, HIV-1 viral suppression may not be effective following accidental intravenous maladministration.	• Training will be provided to all sites on proper injection technique. • Should IM maladministration be suspected at any time (e.g., suspected under or overdose or inadvertent intravenous [IV] dosing), post dose ECG monitoring and vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified • Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all participants. Additionally, 2-hour post dose PK samples will be obtained at a few early timepoints for determination of RPV concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes and virologic response. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of RPV concentrations.
Overall Study Related Risks		
Venipuncture	Participants will be required to have blood samples taken. Risk of bruising, and rarely, infection	• Trained personnel will perform venipuncture
Risks of ECG pad removal	Some discomfort and rash may occur where the ECG pads are removed.	• ECGs will be conducted by appropriately trained personnel and effort made to minimize contact time for application of the pads.
Risk of Treatment Failure	This study employs a novel 2 drug LA ART maintenance regimen for the treatment of HIV-1 infection that remains experimental. Both IM CAB and RPV have demonstrated antiviral activity in large clinical studies and the two-drug combination has demonstrated sustained antiviral activity in studies, LAI116482 and 200056, however the efficacy of Q8W v Q4W dosing remains	• Viral loads and CD4+ cell counts will be closely monitored throughout the study (maintenance and extension phases), allowing for early detection of failing treatment. Where confirmed virological failure occurs, participants would be discontinued from study drugs and transferred to an oral

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	under evaluation. Doses of the CAB LA and RPV LA have been selected to achieve exposures that are expected to maintain virologic efficacy on the basis of available data with the oral and LA formulations. Due to administration error, it is possible that a participant could receive an inadequate dose of CAB LA or RPV LA. Sub-therapeutic concentrations of either CAB LA or RPV LA could lead to virologic failure and possibly the development of viral resistance.	HAART regimen. • Plasma samples will be collected throughout the Maintenance Phase for determination of CAB and RPV concentration and possible pharmacokinetic correlation with virologic response.

DTG + RPV

For safety and risk mitigation for DTG +RPV, you may also refer to the Juluca prescribing information [Juluca Prescribing Information, 2017].

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy [a]
Commercial Juluca [DTG and RPV] Refer to IBs for additional information		
DTG: Hypersensitivity reaction (HSR) and rash **RPV:** Rash	**DTG:** HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported. **RPV:** Rash is a recognized risk for the non-nucleoside reverse transcriptase inhibitors (NNRTI) class; however, the severe rashes defined above that are labeled for efavirenz (EFV) and nevirapine (NVP) were not seen with RPV in	Specific/detailed toxicity management guidance is provided for HSR (Section 8.7.11) and rash (Section 8.7.12). The subject informed consent form includes information on this risk and the actions subjects should take in the event of: 1) a HSR or associated signs and symptoms; or 2) developing any type of rash or skin abnormality. For Grade 3/4 rash, except where the etiology is clear and not associated with study drug or where there is a definitive diagnosis clearly attributable to a concomitant medication

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy [a]
Commercial Juluca [DTG and RPV] Refer to IBs for additional information		
	clinical trials. In Phase III clinical trials, skin events of interest were reported at a lower incidence and grades, and resulted in fewer subject withdrawals, in the RPV group than in the EFV group and were mostly driven by the individual preferred term Rash.	(and not to study drug) or to a concomitant infection, subjects must permanently discontinue study drug and be withdrawn from the study.
DTG & RPV: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	**DTG:** Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG- containing ART, along with inadequate therapy for HBV co-infected subjects, likely contributed to significant elevations in liver chemistries. **RPV:** Hepatic events have been reported in patients receiving a RPV containing regimen. Patients with underlying HBV or HCV, or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations with use of RPV. A few cases of hepatic toxicity have been reported in patients receiving a RPV containing regimen who had no pre-existing hepatic disease or other identifiable risk factors.	Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 7.1.1).
DTG & RPV: Psychiatric disorders	**DTG:** Psychiatric disorders including suicidal ideation and behaviors are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL- or favorable compared with EFV- based regimens. The reporting rate for insomnia was statistically higher for blinded DTG+ abacavir/lamivudine (ABC/3TC) compared to efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) in ING114467; however, this was not duplicated in any other Phase IIb/III study conducted with DTG. **RPV:** In Phase 3 clinical trials the incidence and grading of depressive disorders (regardless of causality), and the incidence of episodes resulting in subject withdrawal, were comparable between the RPV and EFV treatment	Subjects who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating (Section 5.2). Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality will be monitored during this study through the end of the study participation. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior (Section 8.4.6).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy [a]
Commercial Juluca [DTG and RPV] Refer to IBs for additional information		
	groups. Most depressive disorder events in either treatment group were of Grade 1 or 2 intensity. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the RPV arm.	
DTG & RPV: Increased rates of virologic failure/ Observed Resistance	Virologically suppressed subjects switching from oral CAB + RPV to DTG + RPV may experience virologic failure/breakthrough and development of resistance. **DTG:** Week 96 and Week 144 analyses for the Phase III/IIIb clinical studies supported the efficacy findings from earlier analyses, and demonstrated robust maintenance of viral suppression with no finding of HIV-1 resistance in treatment-naïve subjects. **RPV:** In Phase III clinical trials (pooled Week 96 analyses), 3.2% of patients in the RPV arm experienced virologic failure between Week 48 and Week 96 (2.3 % on EFV).	Subjects will have HIV-1 RNA measured at each study visit. Management of subjects experiencing increase in viral load is described in Section 7.1.5.
DTG: Theoretical serious drug interaction with dofetilide and pilsicainide	Co-administration of DTG may increase dofetilide/pilsicainide plasma concentration via inhibition of organic cation transporter (OCT-2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 6.11.2.4).
DTG: Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (Section 8.7.7).
DTG: Creatine Phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	Specific detailed toxicity management guidance is provided for subjects who develop Grade 3 to 4 CPK elevations (Section 8.7.5).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy [a]
Commercial Juluca [DTG and RPV] Refer to IBs for additional information		
RPV: Corrected QT interval (QTc) prolongation	In healthy subjects, supratherapeutic doses of RPV (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram (ECG). RPV at the recommended dose of 25 mg administered once daily is not associated with a clinically relevant effect on QTc.	Subjects who use medications which are associated with Torsades de Pointes are excluded. Day 1 ECG to identify those with pre-existing prolonged QT interval. Per sentinel event management, study drug will be discontinued when a prolonged QT is identified.
RPV: Fat Redistribution	Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving ART. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.	Routine monitoring of adverse reactions will be performed.

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for HIV-infected patients). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of study drug, and will be followed to resolution as per Sponsor's standard medical monitoring practices.
Clinical Safety Data will be routinely reviewed in GlaxoSmithKline (GSK) Safety Review Team meetings. This will include in-stream review of data from this clinical trial on a routine basis, review of aggregate data on a protocol and program basis when available, and review of competitor data from the literature.

2.3.1.1. Other Clinically Relevant Information

Additional details concerning safety observations from clinical studies and for which a causal association has not been established or which are of minimal clinical significance may be found in the Investigator's Brochures (GlaxoSmithKline Document Number RH2009/00003/07 [CAB IB, 2017], RPV IB, 2017, GlaxoSmithKline Document Number RM2007/00683/11 [DTG IB, 2017]).

Adverse Events of Special Interest:

Seizure

Four cases of seizures have occurred in the cabotegravir programme cumulatively through 04 May 2018 (update Date). Two of the cases occurred in HIV uninfected subjects with a prior history of seizure, of which one had CAB drug levels below the level of quantification 6 months prior to the event and one case involved a subject in study 200056 with circumstantial and anecdotal evidence of illicit drug use. Another case occurred in FLAIR in the context of influenza A meningoencephalitis. Overall, there is not convincing evidence that cabotegravir exposure may be causally associated with seizure or with reduction of seizure threshold, due to the low frequency of reports, the confounders present in the cases received to date and lack of any pre-clinical signal or identified plausible mechanism. However, seizure and seizure-like events are considered as AEs of special interest for close monitoring in studies. Subjects with an unstable or poorly controlled seizure disorder will be excluded from study participation.

2.3.2. Benefit Assessment

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

Participants receiving CAB LA + RPV LA are anticipated to benefit from maintenance of virological suppression using LA agents. Participants who receive CAB LA+ RPV LA Q2M dosing will not need to take concomitant daily oral therapy. Adherence in these participants is expected to be improved and will be directly observed during IM injections. Efficacy of this two-drug regimen, as IM agents, has been demonstrated through Week 96 of the ongoing 200056 study. This regimen may continue to offer long term safety and tolerability benefits in these participants.

Participants who will receive PO DTG and RPV are anticipated to benefit from the fact that both are conveniently dosed as a single tablet once daily, without need for a pharmacokinetic (PK) booster, and with limited safety implications resulting from theoretical or actual drug:drug interactions compared to other ART agents (including efavirenz (EFV) and those requiring a PK booster). In addition, the high barrier to resistance observed with DTG should help protect against the development of resistance to both components of the DTG + RPV regimen. Juluca was recently approved as single dose maintenance. Individually, DTG and RPV in combination with other ARVs have demonstrated durable virologic and immunologic response.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with the CAB LA and RPV LA Q2M and DTG + RPV regimens and the study as a whole are justified by the anticipated benefits that may be afforded to virologically suppressed, treatment-experienced participants with HIV-1 infection.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate the antiviral activity of CAB LA + RPV LA every 2 months in suppressed HIV-1 infected antiretroviral therapy ART-experienced participants	Proportion of participants with HIV-RNA ≥50 c/mL as per food and drug administration (FDA) Snapshot algorithm at Month 12
Secondary	
To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every 2 months and oral DTG +RPV	Proportion of participants with plasma HIV-1 RNA <50 c/mL (c/mL) at Month 12

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

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

4. STUDY DESIGN

4.1. Overall Design

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

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

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

Participants in POLAR who successfully complete Week 300 in the LATTE study (without meeting study defined withdrawal criteria) will be given the option to receive either CAB LA + RPV LA (administered Q2M) or oral DTG + RPV daily until study intervention is either locally approved and commercially available within the local sector (including through local public/government health sectors), the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA + RPV LA Q2M is terminated.

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

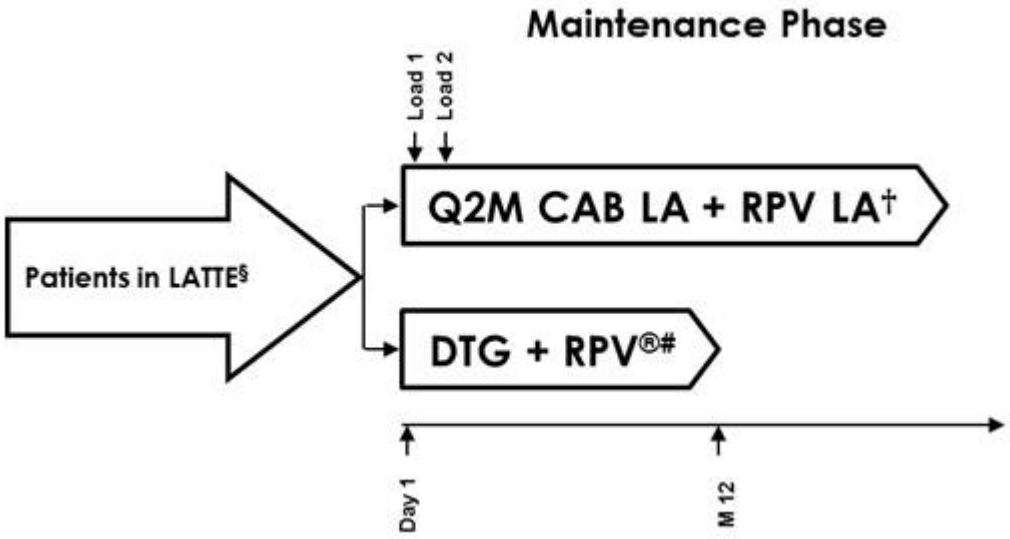
The primary endpoint for the study is the proportion of participants with HIV-RNA greater than or equal to 50 c/mL at Month 12 as per Food and Drug Administration (FDA) Snapshot algorithm using the Intent-to-Treat Exposed (ITT-E) population.

4.1.1. Evaluable Participants

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

4.1.2. Study Schematic

Figure 1 209035 (POLAR) Study Design Schematic



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

4.2. Treatment Groups and Duration

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

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

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

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

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

In addition to the viral load criteria above, if in the opinion of the Investigator, a participant experiences a significant safety event while taking either CAB or RPV, study eligibility will be determined ONLY in consultation with the medical monitor.

Participants ineligible for this study will be withdrawn from LATTE.

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

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

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

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

Participants will continue CAB LA + RPV LA until:

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

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

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

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

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

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

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

4.2.3. LTFU Phase – IM Regimen Only

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

failure is confirmed. Discuss with medical monitor. The LTFU will begin the day of the last CAB LA and/or RPV LA dose and continue for 52 weeks. These participants will not complete a Withdrawal visit, but will instead move directly into the LTFU as per the Time and Events Schedule. In addition, for participants who withdraw during the LTFU, the final visit will be considered the study withdrawal visit.

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

In order to assure that participants have access to HAART during the LTFU, ViiV may supply HAART regionally or reimbursement will be provided as needed during this phase. The LTFU Phase may be shortened or terminated at any time during the study for various reasons, e.g., better understanding of risks of development of resistance as CAB and RPV exposures decline, end of study timings, etc.

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

4.3. Scientific Rationale for Study Design

The design of this study (open-label, multicenter rollover study) will allow for the collection of longer term efficacy, safety and tolerability data for the CAB LA + RPV LA Q2M regimen. This study will also allow participants in the LATTE study who are on the oral CAB 30 mg + RPV 25 mg regimen, which will not be submitted to the regulatory agencies as a maintenance regimen for the treatment of HIV-1 infection, to be placed on a regimen currently being studied for those purposes (CAB LA +RPV LA). Those participants who want to remain on oral 2 drug therapy will be administered the regulatory-approved regimen of oral DTG + RPV for at least a year, until commercial approval of said regimen is met. The primary endpoint, proportion of participants defined as virologic failures by the FDA Snapshot algorithm is recommended in the FDA's 2015 guidance document (FDA, 2015) for assessing efficacy in Switch Trials. The key secondary endpoints, proportion with plasma HIV-1 RNA <50 c/mL at Month 12, is also a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression.

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

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

Participants electing to receive CAB LA + RPV LA Q2M IM administration will be required to participate in clinic visits approximately every 2 months while participants electing to receive oral DTG + RPV administration will be required to participate in clinic visits approximately every 3 months. Importantly, secondary objectives of this study are to understand the acceptability, tolerability, and patient reported preferences to the novel injectable regimen. An unblinded study design supports collection of participant preference data in a way that would not be possible if a double-blind, double-dummy design were implemented. If the Q2M arm were required to receive blinded placebo tablets every day, the value of comparing safety, tolerability, and convenience of Q2M compared to oral administrations would be limited and include overly burdensome visit requirements for those randomized to Q2M administration. Additionally, the perceived value for participants to transition from the LATTE study to POLAR to receive the Q2M regimen would also be limited and may result in loss of patients with prior oral 2 drug regimen experience, thereby limiting the ability to compare and evaluate the experience gained after 6 years of treatment on an oral 2 drug regimen plus Q2M regimen administration within individual participants.

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

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

4.4. Justification for Dose

4.4.1. Long Acting Injectable for Maintenance Phase

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

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

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

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

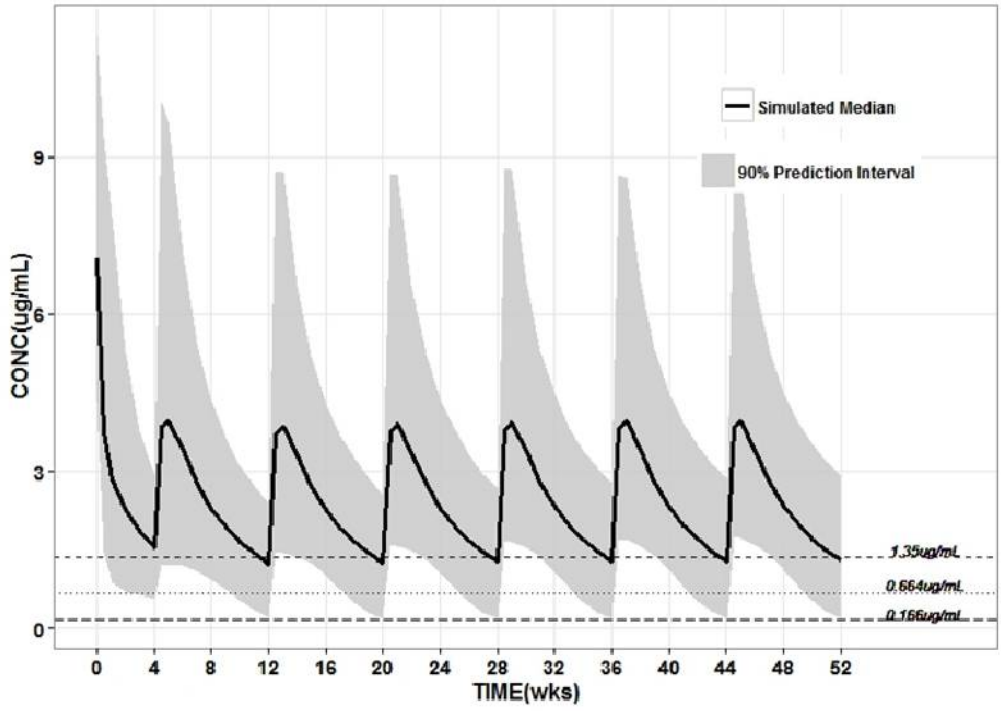
The CAB LA population PK model was updated to include data from CAB LA pre-exposure prophylaxis (PrEP) Study 201120 (ÉCLAIR; GlaxoSmithKline Document Number 2016N269422_00) and Study 200056 (LATTE-2), increasing the original model from 93 participants to 416 participants receiving CAB LA single or repeat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

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

4.4.1.1. CAB LA Q2M

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

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



*Note: current simulations based on interim plasma concentration dataset

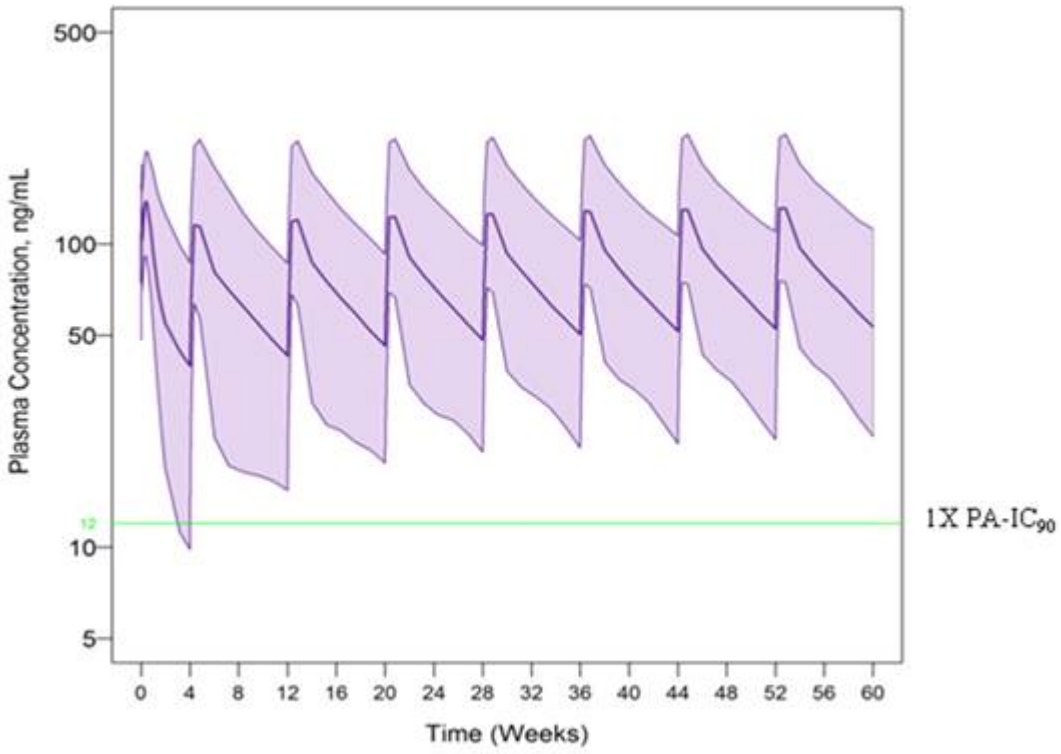
A one-week delay in CAB LA dosing for the Q2M regimen at steady state is predicted to result in ~92% rather than 95% of participants achieving trough concentrations above the PA-IC90, which is considered acceptable.

4.4.1.2. RPV LA Q2M

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

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

Figure 3 Simulated* Median (90% PI) RPV Plasma Concentrations versus Time Profile for the Optimized RPV LA Q8W regimen (900 mg IM Day)



* Note: current simulations based on interim plasma concentration dataset

At steady-state, a one-week delay in dosing for the RPV LA Q2M regimen is predicted to result in a median steady-state Cτ that is approximately 11% lower (48 ng/mL) than for dosing that is administered on schedule, with >99% of subjects still remaining above the RPV PA-IC90. This supports allowance of some flexibility in the dosing regimen similar to what is currently practiced in ongoing LATTE-2 and ATLAS 2M studies.

4.4.1.3. DTG + RPV

To date, the efficacy, PK, safety, and drug interaction potential of DTG and RPV as individual agents have been evaluated in two extensive clinical development programs of Phase I to III clinical trials. As individual agents, DTG and RPV are both approved and marketed as TIVICAY 50 mg once daily and Edurant 25 mg once daily, respectively, the doses used in the current study.

Clinical data showed the absence of a drug:drug interaction between DTG and RPV. Study ING116181 was a Phase I, open-label, crossover study to evaluate the pharmacokinetics and safety of GSK1265744 and RPV and DTG and RPV in healthy adult participants. The study showed that co-administration of RPV with DTG had no clinically meaningful effect on DTG or RPV pharmacokinetics [Ford, 2013].

Co-administration of RPV with DTG had no effect on DTG area under the concentration curve from 0 hours to the time of next dosing (AUC[0-τ]) or maximum concentration (Cmax), and increased DTG Cτ by 22%, while co-administration of DTG with RPV had no effect on RPV AUC(0-τ) or Cmax and increased RPV Cτ by 21%. Hence, based on this data there is no need for a dose adjustment from approved doses when both products are used in combination.

A summary of the overall clinical development for both products is available in the IBs for the respective products [see DTG IB: GlaxoSmithKline Document Number RM2007/00683/11, 2017 and RPV IB, 2017] as well as the Juluca Prescribing Information, 2017.

4.5. End of Study Definition

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

Study Completion

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

- Assigned to either treatment group, completed the Maintenance Phase (Month 12 for DTG +RPV participants only), remaining on study until commercial supplies of CAB LA + RPV LA Q2M or DTG + RPV regimens become locally available or development of CAB LA + RPV LA is terminated;

Additionally, participants will continue this study until:

- the participant no longer derives clinical benefit,
- the participant meets a protocol-defined reason for discontinuation

Participants who withdraw from CAB LA + RPV LA and go into the LTFU Phase will be considered to have prematurely withdrawn from the study intervention.

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

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational regimen or other study intervention that may impact participant eligibility is provided in the current Investigator's Brochures (IB) for CAB (GlaxoSmithKline Document Number RH2009/00003/07) and RPV IB, 2017, Edurant Prescribing Information, 2018 and Juluca Prescribing Information, 2017.

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

5.1. Inclusion Criteria

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

- Be able to understand and comply with protocol requirements, instructions, and restrictions;
- Understand the long-term commitment to the study and be likely to complete the study as planned;
- Be considered appropriate candidates for participation in an investigative clinical trial with oral and intramuscularly injectable medications (e.g., no active substance use disorder, acute major organ disease, or planned long-term work assignments out of the country, etc.).

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

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

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

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

AGE
1. Aged 18 years or older (or ≥19 where required by local regulatory agencies), at the time of signing the informed consent.
SEX
2. A female participant is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin [hCG] test at Day 1), not lactating, and at least one of the following conditions applies: a. ***Non-reproductive*** potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion • Hysterectomy • Documented Bilateral Oophorectomy • Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. b. **Reproductive potential** and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) from 30 days prior to the first dose of study medication, throughout the study, for at least 30 days after discontinuation of all oral study medications, and for at least 52 weeks after discontinuation of CAB LA and RPV LA. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.
INFORMED CONSENT
3. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Eligible participants or their legal guardians (and next of kin when locally

required), must sign a written Informed Consent Form before any protocol-specified assessments are conducted. Enrolment of participants who are unable to provide direct informed consent is optional and will be based on local legal/regulatory requirements and site feasibility to conduct protocol procedures.
Other Inclusion Criteria:
4. Must have been on oral CAB 30 mg + RPV 25 mg regimen through at minimum Week 300 of the LATTE study as per LATTE protocol dosing requirements and until Day 1 of the POLAR study. Any disruptions in dosing during LATTE must be discussed with the Medical Monitor for a final determination of eligibility. 5. Plasma HIV-1 RNA <50 c/mL at Week 300. If participant has plasma HIV-1 RNA ≥50 c/mL at Week 300 in LATTE, a single repeat to determine eligibility may be allowed ONLY after consultation with the medical monitor.

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

5.2. Exclusion Criteria

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

Participants transitioning from LAI116482 (LATTE)
1. During the last 6 months of participation in LATTE, consecutive (2 or more sequential) plasma HIV-1 RNA measurements ≥50 c/mL 2. During the last 6 months of participation in LATTE, any HIV-1 RNA measurement ≥200 c/mL
Exclusionary medical conditions
3. Any evidence of a current Center for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy. 4. Participants with moderate to severe hepatic impairment determined by Child-Pugh classification. 5. Any pre-existing physical or mental condition (including substance use disorder) which, in the opinion of the Investigator, may interfere with the participant's

ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participant

6. Participants determined by the Investigator to have a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder. A participant with a prior history of seizure may be considered for enrolment if the Investigator believes the risk of seizure recurrence is low.
7. Participants who, in the investigator's judgment, pose a significant suicide risk. Participant's recent history of suicidal behavior and/or suicidal ideation should be considered when evaluating for suicide risk
8. The participant has a tattoo or other dermatological condition overlying the gluteus region which may interfere with interpretation of injection site reactions
9. Evidence of Hepatitis B virus (HBV) infection based on the results of testing for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs) and HBV DNA as follows:
    a. •Participants positive for HBsAg are excluded;
    b. •Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded

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

10. Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; participants who are anticipated to require HCV treatment within 12 months must be excluded. (HCV treatment on study may be permitted, following consultation with the medical monitor)
11. Participants with HCV co-infection will be allowed entry into this study if:
    a. Liver enzymes meet entry criteria
    b. HCV Disease has undergone appropriate work-up, and is not advanced. Additional information (where available) on participants with HCV co-infection at screening should include results from any liver biopsy, Fibroscan, ultrasound, or other fibrosis evaluation, history of cirrhosis or other decompensated liver disease, prior treatment, and timing/plan for HCV treatment.
    c. In the event that recent biopsy or imaging data is not available or inconclusive, the Fib-4 score will be used to verify eligibility
        i. Fib-4 score >3.25 is exclusionary
        ii. Fib-4 scores 1.45 – 3.25 requires Medical Monitor consultation

        Fibrosis 4 Score Formula:

        (Age x AST) / (Platelets x (sqr [ALT])
12. Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice or cirrhosis), known biliary abnormalities (with the

exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment) 13. History of liver cirrhosis with or without hepatitis viral co-infection. 14. Ongoing or clinically relevant pancreatitis 15. Clinically significant cardiovascular disease, as defined by history/evidence of congestive heart failure, symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or any clinically significant cardiac disease 16. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the Study medical monitor for inclusion of the participant prior to randomization 17. Any condition which, in the opinion of the Investigator, may interfere with the absorption, distribution, metabolism or excretion of the study drugs or render the participant unable to receive study medication 18. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class. In addition, if heparin is used during PK sampling, participants with a history of sensitivity to heparin or heparin-induced thrombocytopenia must not be enrolled 19. Current or anticipated need for chronic anti-coagulation with the exception of the use of low dose acetylsalicylic acid (≤325 mg) or hereditary coagulation and platelet disorders such as haemophilia or Von Willebrand Disease. 20. Corrected QT interval (QTc (Bazett)) >450 msec *or* QTc (Bazett) >480 msec for subjects with bundle branch block.
Exclusionary Laboratory Values or Clinical Assessments (a single repeat to determine eligibility is allowed)
21. Any verified Grade 4 laboratory abnormality over the last 6 months in LATTE. A single repeat test is allowed to verify a result 22. Any acute laboratory abnormality over the last 6 months in LATTE, which, in the opinion of the investigator, would preclude the participant's participation in the study of an investigational compound 23. Alanine aminotransferase (ALT) ≥5 × ULN *or* ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) over the last 6 months in LATTE
Concomitant Medications
24. Exposure to an experimental drug (with the exception of those in the LATTE study including CAB and RPV) or experimental vaccine within either 30 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to Day 1 of this study; 25. Treatment with any of the following agents within 28 days of Day 1:

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

26. Use of medications which are associated with Torsade de Pointes must be discussed with the Medical Monitor to determine eligibility. (See SPM for a list of relevant medications)
27. Participants receiving any prohibited medication and who are unwilling or unable to switch to an alternate medication. Note: Any prohibited medications that decrease CAB, RPV and/or DTG concentrations should be discontinued for a minimum of four weeks or a minimum of three half-lives (whichever is longer) prior to the first dose and any other prohibited medications should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose

5.2.1. Additional Eligibility Criteria

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

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

5.3. Lifestyle Considerations

No restrictions are required.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

The term 'study intervention' is used throughout the protocol to describe any combination of products received by the participant as per the protocol design. **Study intervention is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol**. Study intervention may therefore refer to the individual study interventions or the combination of those study interventions.

Investigational product (IP) in this protocol refers to the investigational study drugs Oral Cabotegravir, Cabotegravir LA, Oral Rilpivirine and Rilpivirine LA. These will be supplied by GlaxoSmithKline/ViiV Healthcare and Janssen Pharmaceuticals, respectively. Commercially available DTG + RPV (Juluca) will be supplied by GlaxoSmithKline/ViiV Healthcare as fixed dose combination tablets.

Participants entering the Long-Term Follow-Up Phase will not have their selected HAART provided as clinical trial material. The selected HAART will be recorded on the Concomitant Antiretroviral Therapy (ConART) eCRF page.

6.1.1. Formulations of CAB + RPV

6.1.1.1. Cabotegravir Tablets (CAB)

CAB is manufactured by GlaxoSmithKline and is formulated as white to almost white oval shaped film coated 30 mg tablets for oral administration, packaged in high density polyethylene (HDPE) bottles with desiccant and child-resistant closure that include an induction seal. CAB tablets will be packaged in bottles of 30 tablets. Participants must keep all IP in its original pack container. GSK will notify sites if and when data are available to support the use of pill boxes. The recommended storage conditions, and expiry date where required, are stated on the product label.

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

6.1.1.2. Rilpivirine Tablets (RPV)

RPV is provided by Janssen Research & Development, LLC, a division of Janssen Pharmaceuticals, as 25 mg tablets that are off-white, round, biconvex, film-coated and debossed on one side with "TMC" and the other side with "25". RPV is manufactured by Janssen-Cilag S.p.A, Latina, Italy. RPV will be provided as a globally marketed product which includes approvals in the US and the European Union. RPV will be overlabeled and packaged in bottles of 30 tablets. The recommended storage conditions, and expiry date where required, are stated on the product label.

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

6.1.1.3. Cabotegravir Injectable Suspension (CAB LA)

CAB LA (GSK1265744 LA) is manufactured by GlaxoSmithKline and is a sterile white to slightly pink suspension containing 200 mg/mL of GSK1265744 as free acid for administration by intramuscular (IM) injection. The product is packaged in a glass vial with a 13 mm gray stopper and aluminum seal. Each vial is for single-dose use containing a withdrawable volume of 2.0 mL (400 mg) or 3 mL (600 mg) and does not require dilution prior to administration. The recommended storage conditions, and expiry date where required, are stated on the product label.

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

6.1.1.4. Rilpivirine Injectable Suspension (RPV LA)

RPV LA (also named JNJ-16150108-AAA), 300 mg/mL Extended Release Suspension for Injection (G001), is provided by Janssen Research & Development, LLC, a division of Janssen Pharmaceuticals, as a sterile white suspension containing 300 mg/mL of RPV as the free base. The route of administration is by intramuscular (IM) injection. RPV LA is packaged in a single use 4 mL glass vial with a 13 mm grey stopper and aluminum seal. Each vial contains a nominal fill of 2.0 mL (600 mg) or 3.0 mL (900 mg), and does not require dilution prior to administration. The recommended storage conditions, and expiry date where required, are stated on the product label.

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

6.1.2. Tablet Formulation of DTG + RPV (Juluca)

Each Juluca tablet contains 50 mg of dolutegravir and 25 mg of rilpivirine, and is a pink, oval, film-coated, biconvex tablet debossed with “SV J3T” on one side. Bottle of 30 tablets with child-resistant closure (contains a desiccant) NDC 49702-242-13.

The recommended storage conditions, and expiry date where required, are stated on the product label.

6.2. Treatment Assignment

Participants transitioning from the LATTE study on oral CAB + RPV treatment will transition to their elected treatment regimen, either Q2M administration of CAB LA + RPV LA or oral DTG + RPV single tablet regimen. Regardless of treatment arm, the

investigator should instruct all participants on the importance of treatment adherence. This study has an open-label design. Dosing is outlined in Table 2.

Table 2 Dosage and Administration

Maintenance Phase (Day 1 to End of Study+)	
Q2M Arm- Transitioning from LATTE	
First Injections (Loading Doses) – Day 1 and Month 2	
Day 1	• Receive last dose of oral CAB + RPV regimen • Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Month 2	• Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Maintenance Injections – every 2 months (Q2M) following Month 2	
Month 4 to End of Study+ (two 3 mL injections every 2 months)	• Receive CAB LA 600 mg given as 1 X **3** mL IM injection • Receive RPV LA 900 mg given as 1 X **3** mL IM injection
Oral DTG + RPV Arm – Transitioning from LATTE	
Day 1 to Month 12+ (once daily FDC tablet taken with food)	• Take one tablet of DTG 50 mg + RPV 25 mg once daily
+Until locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of CAB LA or RPV LA is terminated	

6.3. Blinding

This will be an open-label study and therefore no blinding is required.

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- In accordance with local regulatory requirements, the investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records). The amount of IP dispensed and/or administered to study participants, the amount returned by study participants, and the amount received from and returned to GSK must be documented.
- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.
- Product accountability records must be maintained throughout the course of the study.

IP accountability will be evaluated using pill counts of unused IP for participants receiving oral treatment (oral CAB and oral RPV). This assessment will be conducted each time the participant receives a new (refill) supply of IP through the withdrawal or study completion.

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

No special preparation of study intervention is required for DTG + RPV.

6.5.1. Dosing Considerations for CAB LA + RPV LA

Vials of CAB LA and RPV LA are each supplied as a suspension and need no further dilution or reconstitution. Since RPV LA requires refrigeration, sites should allow the

vial to come to approximately room temperature prior to injecting. The vials should be gently inverted a few times to re-suspend sediments and allow bubbles to subside, and then use a syringe to withdraw the required volume of suspension for IM injection.

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

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

At the Day 1 visit, participants transitioning from oral CAB + RPV should be dosed with the IM regimen within 2 hours of taking the last oral regimen dose where possible.

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

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

6.6. Compliance with Study Intervention Administration

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

When participants self-administer oral study interventions at home, compliance with CAB + RPV and DTG + RPV dosing will be assessed through querying the participant during the site visits and documented in the source documents and CRF. IP accountability will be evaluated using pill counts of unused IP (CAB, RPV and DTG + RPV tablets). This assessment will be conducted each time the participant receives a new

(refill) supply of oral study medication or any oral bridging phase. A record of the number of CAB, RPV and DTG + RPV tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Treatment start and stop dates will also be recorded in the eCRF.

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

6.7. Dose Modifications

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during the study beyond what is allowed within the protocol or directly approved by the study Medical Monitor. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements is essential and required for study conduct. See Section 4.4 for the justification of dose.

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

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

6.7.1. Protocol Permitted Substitutions

6.7.1.1. Oral Bridging

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

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

6.8. Interruption of Study Intervention and Visit/Dosing Windows

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

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

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

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

6.8.1. IM Dosing

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

IM dosing is expected to occur during the week in which the participant's projected visit falls (as according to the date of the first injection). The first injections for participants from LATTE on oral CAB + RPV will occur at Day 1.

Since the first injection visit (Day 1) will determine the future injection visit schedule for participants, planning for the first injection visit date (within allowed visit windows) should take into consideration the availability of the participants to adhere to future visit windows (planned vacations, business trips, *etc*.).

CAB LA + RPV LA dosing for participants transitioning from oral CAB + RPV is as follows:

All injections should be planned as single injections per drug.

6.8.1.1. IM injections every 2 months (Q2M):

On Day 1, participants will return to the clinic, take the last dose of their oral (CAB 30 mg + RPV 25 mg), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV).

The second loading injection will be administered at Month 2 (CAB LA 600 mg + RPV LA 900 mg, with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring every 2 months thereafter. The dosing window for the second injection allows administration between -7 days of the proposed Month 2 injection visit and the proposed Month 2 injection visit date, but preferably not later than the proposed Month 2 injection visit date. After Month 2, a dosing window (±7 days) for injections is stipulated. the Medical Monitor must be contacted to discuss individual participant case management if a dose has to be administered outside of the window.

6.8.2. Oral Dosing

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

Visits for participants in LTFU are expected to occur as projected according to the last injection.

6.9. Treatment of Study Intervention Overdose

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

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

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

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

For the purposes of this study, an overdose is not an AE (refer to Section 12.4.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a SAE (see Section 12.4.2).

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

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

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

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

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

6.10. Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study intervention. Participants who have successfully completed IM dosing and 12 months of oral DTG + RPV will continue to have access to both CAB LA and RPV LA and oral DTG + RPV until study intervention is either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated.

6.11. Concomitant Medications and Non-Drug Therapies

Participants must be advised to notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications. Concomitant medications (prescription and non-prescription) will be permitted during the course of the study at the investigator's discretion (except for prohibited medications described in Section 6.11.2 and should be administered only as medically necessary during the study. All concomitant medication, blood products, and vaccines taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name, route, and the dates of administration are to be recorded.

For DTG + RPV, The investigator should evaluate any potential drug:drug interactions at every visit, including reviewing the most current version of the U.S and local prescribing

information for DTG and RPV, especially if any new concomitant medications are reported by participants.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.11.1. Permitted Medications and Non-Drug Therapies

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

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

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

Antacid and H2 Antagonist Use:

The most restrictive dosing requirements must be taken into consideration to account for the co-administration of oral CAB and RPV. The marketed approved recommendation for administration of antacids and H2 antagonists with the FDC of DTG + RPV incorporates the most restrictive dosing requirements.

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

Concurrent administration of multivitamins is acceptable.

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

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

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

6.11.2. Prohibited Medications and Non-Drug Therapies

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

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Exclusion Criteria: Section 5.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SPM). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis (James, 2009).
- Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided due to their immunosuppressive effect; however, short treatment courses with oral prednisone/ prednisolone/methylprednisolone (e.g. adjunctive treatment of Pneumocystis pneumonia with ≤ 21 days of tapering prednisone) are allowed. A single dose of systemic dexamethasone is permitted (more than a single dose in a treatment course may cause significant decrease in RPV plasma concentration and is prohibited). Topical, inhaled or intranasal use of glucocorticoids will be allowed.
- Hepatitis C infection therapy is allowed, and interferon-based HCV therapy or use of any drugs that have a potential for adverse drug:drug interactions with study intervention is prohibited throughout the entire study.

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

6.11.2.1. Concurrent with CAB and/or RPV and DTG + RPV

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

- Carbamazepine
- Oxcarbazepine

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

6.11.2.2. Concurrent with oral RPV

In addition to the medications listed in Section 6.11.2.1, participants must discontinue the following (or change to an allowable alternative) while receiving treatment with oral RPV:

- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole;
- systemic dexamethasone (more than a single dose)

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

6.11.2.3. Concurrent with either CAB LA or RPV LA

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

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

6.11.2.4. Concurrent with DTG + RPV

In addition, for participants receiving DTG +RPV, the following is prohibited:

- Dofetilide and pilsicainide (as DTG may inhibit renal tubular secretion resulting in *increased* dofetilide concentrations and potential for toxicity).

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

Refer to the Juluca prescribing information [Juluca Prescribing Information, 2017] for a full list of prohibited medications.

6.11.2.5. Prohibited Medications for Participants Receiving HAART during the Long-Term Follow-Up Phase

For participants taking HAART during the Long-Term Follow-Up Phase, refer to local prescribing information for details regarding concurrent therapies.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

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

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

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

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

- Adverse event / Serious adverse event
- Protocol deviation
- Intolerability of injections
- Participant lost to follow-up
- Participant or Investigator non-compliance;
- Termination of the study by the Sponsor
- At the request of the participant, Investigator, GSK or ViiV Healthcare;
- The participant requires concurrent prohibited medications during the course of the study. The participant may remain in the study if in the opinion of the Investigator and the medical monitor; such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the participant.

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

- Virologic withdrawal criteria as specified in Section 7.1.3 are met;
- Participant requires substitution of ART;
- Participant requires substitution or dose reduction of CAB LA, RPV LA (oral bridging supply and potential for a second loading dose may be permissible following discussion with the Medical Monitor) and oral DTG + RPV.
- Liver toxicity where stopping criteria are met and no compelling alternate cause is identified (see Section 7.1.1);
- Renal toxicity is met and no compelling alternate cause is identified;
- Corrected QT interval (QTc) >550 msec from three or more tracings separated by at least 5 minutes and considered causally related to IP. *Note: ECGs are not routinely conducted in this study*.
- Grade 4 clinical AE considered causally related to study drug;
- Participant has a Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement and no compelling alternative cause is identified
- Pregnancy (intrauterine), regardless of termination status of pregnancy.
- Participant withdrew consent

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

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

If a participant is prematurely or permanently withdrawn from the study, the procedures described in the Time and Events Table for the in-clinic Withdrawal visit are to be performed. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study medication for participants with ongoing AEs, and serious adverse events (SAEs) related & not related to study drug and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit.

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

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

a. The site must attempt to contact the participant and re-schedule the missed visit as soon as possible.

b. The site must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

c. In cases where the participant is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and if necessary a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

d. Should the participant continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

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

7.1. Discontinuation of Study Intervention

Participants unable to manage drug toxicity or tolerate investigational product (IP, either formulations of CAB or RPV, or DTG + RPV) must have IP discontinued. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART enter the LTFU Phase for 52 weeks of follow up (see Section 4.2.3).

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

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

- ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin, bilirubin fractionation required).
- NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, sites should evaluate the presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a participant meets the criterion of total bilirubin ≥2xULN, then the event meets liver stopping criteria.
- ALT ≥8xULN.
- ALT ≥3xULN (if Baseline ALT is <ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR;

- ALT ≥3x Baseline ALT (if Baseline ALT is >ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5xULN and <8xULN that persists ≥2 weeks (with bilirubin <2 ULN & no signs or symptoms of acute hepatitis or hypersensitivity).

ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks.

7.1.1.1. Liver Chemistry Stopping Criteria, Participant Management and Follow-up

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

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

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

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

- Viral hepatitis serology including:
    - Hepatitis A immunoglobulin M (IgM) antibody;
    - Hepatitis B surface antigen (HBsAg) and Hepatitis B Core Antibody (IgM);
    - Hepatitis C RNA;
    - Hepatitis E IgM antibody;
    - Cytomegalovirus IgM antibody;
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);

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

7.1.1.2. Liver Event Adjudication Committee

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

7.1.1.3. Liver Chemistry Stopping Criteria – Restart / Rechallenge

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study treatment unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and

- Separate consent for treatment restart/rechallenge is signed by the participant

If VSLC approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

7.1.1.3.1. Drug Restart / Rechallenge. Following Liver Events that are Possibly Related and not related to Study intervention

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Hunt, 2010; Papay, 2009]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010].

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by the VSLC for drug rechallenge can be considered where:

- Principal Investigator (PI) requests consideration of rechallenge with study treatment for a subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If the restart/rechallenge is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.

- Subjects approved by the VSLC for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol defined liver chemistry stopping criteria, study drug must be permanently discontinued.
- The Medical Monitor and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge
- Any adverse events should be recorded on the appropriate eCRF(s), and reported where applicable, as per Section 8.5.

7.1.1.3.2. Drug Restart Following Transient Resolving Liver Events Not Related to Study intervention

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by the VSLC for drug restart can be considered where:

- Investigator requests consideration for study treatment restart if Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <5xULN).
- Furthermore, there should be no evidence of fever, rash, eosinophilia, hypersensitivity, alcoholic hepatitis or possible study treatment-induced liver, and the drug should not be associated with HLA markers of liver injury. (If restart of TRIUMEQ or any other abacavir- containing product is being considered then the Subject must be HLA-B*5701 negative).
- Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If restart of drug is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Subjects approved by the VSLC for restarting IP must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as

long as clinically indicated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions..
- The Medical Monitor and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart
- Any adverse events should be recorded on the appropriate eCRF(s), and reported where applicable, as per Section 8.5.

7.1.2. QTc Stopping Criteria

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

If an alternative cause of the QT prolongation is determined (e.g., participant receiving drug known to cause prolonged QT or TdP), the IP may be restarted (or continued) after consultation and agreement with the Medical Monitor. RPV and RPV LA should not be administered to participants who are receiving a drug known to be associated with TdP.

When performing ECGs, the *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for, and discontinuation from, the study. This formula may not be changed or substituted once the participant has been enrolled.

For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.

Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

7.1.3. Virologic Failure

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

7.1.4. Definition of Protocol-Defined Confirmed Virologic Failure

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

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

7.1.5. Managing Virologic Failure

Following study entry, no changes, or intensification of ART will be permitted prior to protocol-defined virologic failure, outside of the planned protocol regimens. Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic failure. Baseline plasma HIV-1 RNA is the assessment completed on study Day 1. The definition of confirmed virologic failure does not apply to participants in the LTFU Phase. These participants will be followed for the emergence of viral resistance.

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

7.1.5.1. HIV-1 RNA Blips

HIV-1 RNA "blips" are not usually associated with subsequent virologic failure [DHHS, 2016]. Although the implications of persistent HIV-1 RNA levels between the lower level of detection and <200 c/mL are unclear, the risk of emerging resistance is believed to be relatively low.

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

Participants who have a HIV-1 RNA ≥50 c/mL and <200 c/mL at the key analysis timepoints (Month 12 and End of study must return to the clinic as soon as possible (but no later than 4 weeks after the date of the Month 12 and End of study visit, respectively) for a repeat HIV-1 RNA test such that the result falls within the same analysis window.

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

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

7.1.5.2. Suspected Virologic Failure

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

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

- Confirmatory testing should be scheduled within 2 to 4 weeks following resolution of any intercurrent illness, during which time the participant should receive full dose of all study intervention.
- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the participant should receive full dose of all study intervention.
- If therapy is interrupted* due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dose of all study intervention.
- The participant should have received full dose of study intervention for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

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

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

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

7.1.5.3. Confirmed Virologic Failure

Participants with CVF must be discontinued from study intervention. However, participants who have received at least one dose of CAB LA or RPV LA prior to confirming virologic failure will remain in the study on oral HAART in the LTFU Phase.

A plasma sample from the suspected virologic failure visit as well as Day 1 (if baseline HIV-1 RNA level ≥200 c/mL) will be sent for genotypic and phenotypic resistance testing and the result made known to the Investigator when available. A plasma sample from the confirmation visit will be obtained for storage. This sample may be used for possible future analyses, e.g., for genotypic and phenotypic analyses of participants who experience virologic failure.

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 8.1).

The following points must be noted:

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

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

8.1. Time and Events Table

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

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

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

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

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

a. The Day 1 visit will take place during Week 312 (or Week 324 in the event of unavoidable delays) of the LATTE study, the participant's last week on study. LATTE participants eligible for POLAR study dosing will take final dose of CAB 30 mg + RPV 25 mg in the clinic within 2 hours of the Q2M IM regimen. See Section 6.1 for IM dosing administration as loading doses are required. (Day 1=1st loading dose; Month 2=2nd loading dose)
b. Continue this pattern for visits for the remainder of the study. For example, Month 28 will be conducted just like Month 20, Month 30 will be conducted just like Month 22 and so on.
c. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for participant management.
d. Measure vital signs after about 5 minutes of rest in a semi-supine position.
e. Height collected at Day 1 only.
f. On Day 1, ECGs should be performed in triplicate at least 5 minutes apart and following 5 minutes of rest in a semi-supine position within 1 hour prior to first dose. Also on Day 1, a 2-hour post dose ECG will be performed for all participants. The 2-hour post dose ECG on Day 1 can also be used for the LATTE Week 312 (or Week 324, if needed) visit. ECG evaluations at other visits should be obtained after dosing, preferably 2-4 hours post dosing.
g. A (-) urine pregnancy test is required prior to any injection and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), participant will need to be WD.
h. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures.
i. Fast overnight; however, a minimum of a 6 hour fast is acceptable.
j. Take PK samples pre-dose.
k. Q2M Injections are 1 x CAB LA 600 mg IM + 1 x RPV LA 900 mg IM. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. **IM dosing is expected to occur during the month in which the participant's projected visit falls (as according to the Day 1 visit). An additional (+ or -) 7 day window from date of projected visit is stipulated for IM dosing. All decisions regarding dose interruption/ resumption must be discussed with the medical monitor in advance.**
l. Or Long-Term Follow Up
m. Follow Up Visit - Conduct ~4 weeks after the last dose of IP if not entering Long-Term Follow Up and only if the participant has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.

8.1.2. Time and Events Table for DTG + RPV Administration

Procedures for DTG+RPV	Day 1 [a]	Month 3	Month 6	Month 9	Month 12	WD [j]
Written Informed Consent	X					
Demography	X					
Eligibility Verification	X					
Physical Exam	X					
Medical History	X					
CDC Classification	X					
RPR	X					
Symptom Directed Physical Exam and Medical Assessment [b]		X	X	X	X	X
Vital Signs (BP, HR) [c]	X	X	X	X	X	X
Weight, Height & BMI [d]	X	X	X	X	X	X
HIV Associated Conditions, AE and SAE Assessments, Con Meds	X	X	X	X	X	X
12-Lead ECG [e]	X				X	X
HIV-1 RNA	X	X	X	X	X	X
CD4+	X	X	X	X	X	X

Notes

a. The Day 1 visit will take place during Week 312 (or Week 324 in the event of unavoidable delays) of the LATTE study, the participant's last week on study. LATTE participants eligible for POLAR study dosing will take final dose of CAB 30 mg + RPV 25 mg in the clinic. See Section 6.2 for dosing administration.
b. Physical exams should be conducted as part of normal routine clinical care but data will not be collected in the eCRF. Medical assessments include any decisions the study staff must make for participant management.
c. Measure vital signs after about 5 minutes of rest in a semi-supine position.
d. Height collected at Day 1 only.
e. On Day 1, ECGs should be performed in triplicate at least 5 minutes apart and following 5 minutes of rest in a semi-supine position within 1 hour prior to first dose. Also on Day 1, a 2-hour post dose ECG will be performed for all participants. The 2-hour post dose ECG on Day 1 can also be used for the LATTE Week 312 (or Week 324, if needed) visit. ECG evaluations at other visits should be obtained after dosing, preferably 2-4 hours post dosing.
f. Plasma for storage samples are collected for possible future analyses, back-up in cases of loss/damage in transit and geno/pheno analyses for virologic failures.
g. A (-) urine pregnancy test is required prior to any administration of drug and as required by medical monitor after a treatment interruption. A (+) urine test should be confirmed with a stat serum test. If (+), participant will need to be WD.
h. Fast overnight; however, a minimum of a 6 hour fast is acceptable.
i. DTG 50 mg + RPV 25 mg. Administer daily with food
j. Follow Up Visit - Conduct ~4 weeks after the last dose of IP and only if the participant has ongoing AEs or lab abnormalities at the last on-study visit. May be conducted by telephone.

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

8.1.3. Time and Events Table for Long Term Follow Up

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

8.2. Baseline Assessments

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

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

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

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

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

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

- intravenous drug use history;

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

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

- psychiatric (e.g., depression);

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

- neurologic disorders

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

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

8.3. Efficacy Assessments

8.3.1. Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events schedule (Section 8.1). Methods to be used may include but are not limited to the Abbott RealTime HIV-1 Assay lower limit of detection (LLOD) 40 c/mL. In some cases, (e.g., where the HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods will be used to further characterize HIV-1 RNA levels.

8.3.2. Lymphocyte Subsets, CD4+ and CD8+

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts, ratios) according to Time and Events schedule (Section 8.1) and Laboratory Assessments (Section 8.4.2).

8.3.3. HIV Associated Conditions

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

8.4. Safety Assessments

8.4.1. Clinical Evaluations

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

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

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

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

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

8.4.2. Laboratory Assessments

All protocol required laboratory assessments, as defined in the Time and Events Schedule (see Section 8.1), must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labeled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

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

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

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

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

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

Labs will be automatically graded by the central lab according to the DAIDS toxicity scales (See Section 12.3 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events").

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

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

Table 3 Safety Laboratory Assessments

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

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

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

8.4.3. Physical Examinations

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

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

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

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

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

8.4.4. Vital Signs

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

8.4.5. Electrocardiograms

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

8.4.6. Suicidal Ideation and Behaviour Risk Monitoring

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidal ideation or behavior. In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some participants being treated with INIs including DTG. Additionally, depression and anxiety has been reported in some participants being treated with RPV. Therefore, it is appropriate to monitor and closely observe participants prospectively before and during treatment for suicidal ideation and/or behavior, or any other unusual changes in behavior. It is recommended that the Investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including

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

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

8.4.7. Pregnancy

8.4.7.1. Pregnancy testing

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

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

8.4.7.2. Time Period for Collecting Pregnancy Information

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

Female participants that have received at least one dose of CAB LA or RPV LA and do not enter the LTFU Phase should use a highly-effective method of contraception (see the SPM and Appendix 5 (Section 12.5) for a listing of examples of highly-effective hormonal contraception) until at least 52 weeks after the last dose of study drug. If a participant becomes pregnant within 52 weeks of the last dose of study drug the participant should notify the study site.

8.4.7.3. Action to be Taken if Pregnancy Occurs

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

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. The investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 12.5, Appendix 5.

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

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

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

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

8.5. Adverse Events and Serious Adverse Events

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

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

8.5.1. 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 intervention until the final follow-up contact, at the timepoints specified in the Time and Events Table (Section 8.1).
- Medical occurrences that begin prior to the start of study intervention but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.

- The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.4, Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify GSK.

8.5.2. Method of Detecting AEs and SAEs

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

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

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

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 8.7) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 7). Further information on follow-up procedures is given in Section 12.4, Appendix 4).

8.5.4. Prompt Reporting of Serious Adverse Events and Other Events

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to the medical monitor as described in Table 4 once the investigator determines that the event meets the protocol definition for that event. Any seizure or suspected seizure should be reported in an expedited manner, as noted in Table 4.

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

Table 4 Reporting of Serious Adverse Events and Other Events

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

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

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

SAE reporting to GSK via electronic data collection tool

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

The method of recording, evaluating, and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to the medical monitor are provided in the SPM. Procedures for post study AEs/SAEs are provided in the SPM. Primary and

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

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

Disease related events (DREs) or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 12.8) can be serious/life threatening and will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE. However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

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

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

8.5.6. Regulatory Reporting Requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

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

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

8.5.7. Cardiovascular and Death Events

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

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

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

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

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

8.5.8. Death Events

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

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

8.6. Toxicity Management

Adverse events that occur during the trial should be evaluated by the Investigator and graded according to the Division of AIDS (DAIDS) toxicity scales (See Section 12.3. "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events"). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 8.5 and Section 12.4.

8.6.1. Treatment Interruption Due to an Adverse Event

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

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

Guidance is provided below on general participant management and IP interruptions based on the severity of the AE. Information regarding permitted substitutions \ is provided in Section 6.7.1.1. All changes in the IP regimen must be accurately recorded in the participant's eCRF.

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

8.6.2. Grade 1 or Grade 2 Toxicity/Adverse Event

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

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

8.6.3. Grade 3 Toxicity/Adverse Event

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

- If the Investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by IP, dosing may continue after discussion with the Medical Monitor.
- Participants who develop a Grade 3 AE or toxicity, which the Investigator considers related or possibly related to the IP, should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, IP may be re-started.
- Should the same Grade 3 AE recur within 28 days in the same participant, the IP should be permanently discontinued and the participant withdrawn from study.
- Participants experiencing Grade 3 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and to have withdrawal study evaluations completed. A follow-up visit should be performed 4 weeks after the last dose of IP. Any participant receiving at least one dose of CAB LA and/or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the LTFU Phase for 52 weeks of follow up.
- Participants with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue IP if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 8.7.1). Isolated Grade 3 lipid abnormalities do not require withdrawal of IP.

8.6.4. Grade 4 Toxicity/Adverse Event

- Participants who develop a Grade 4 AE or toxicity must have IP permanently discontinued. However, if the Investigator has compelling evidence that the AE is not causally related to the IP, dosing may continue after discussion with, and assent from, the Medical Monitor. Participants should be rechecked each week until the AE returns to Grade 2.
- Participants experiencing Grade 4 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP /

Withdraw will initiate treatment with HAART and enter the LTFU Phase for 52 weeks of follow up.

- Participants with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue therapy if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 8.7.1). An in-clinic follow-up visit will be performed approximately 4 weeks after the last dose of study medication if AEs, SAEs, or laboratory abnormalities considered potentially harmful to the participant are ongoing at the last on-study visit. Isolated Grade 4 lipid abnormalities do not require withdrawal of IP.

8.7. Specific Toxicities/Adverse Event Management

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

Participants who permanently discontinue study drug for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-up study evaluations as noted in Section 8.5.3.

8.7.1. Liver Chemistry Stopping and Follow-up Criteria

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

8.7.2. Diarrhea

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

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

least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the LTFU Phase for 52 weeks of follow up.

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

8.7.3. Hypertriglyceridemia/ Hypercholesterolemia

Samples for lipid measurements **must** be obtained in a fasted state according to the Time and Events table (Section 8.1). Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive IP. Clinical management of participants with hypertriglyceridemia/hypercholesterolemia should **not** be based upon non-fasting samples (obtained in the fed state). A confirmatory fasting triglyceride and/or cholesterol level should be obtained prior to the institution of medical therapy for hyperlipidemia. Isolated Grade 3 and Grade 4 lipid abnormalities do not require withdrawal of IP.

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

8.7.4. Seizures

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

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

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

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

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

8.7.5. Creatine Phosphokinase (CPK) Elevation

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

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

8.7.6. Lipase Elevations and Pancreatitis

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

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

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

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

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

Approval by VSLC for drug restart can be considered where:

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

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

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

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

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

Refer to Section 12.3, U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [March 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf

Refer to Section 12.7, Appendix 7: Liver Safety – Study intervention Restart Guidelines for further details.

8.7.7. Decline in Renal Function

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

Participants who have a decline in the estimated GFR (using the CKD-EPI method) of >50% from Baseline must return for a confirmatory assessment as soon as possible [Levey, 2009]. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios should also be done at this confirmatory visit. If the estimated GFR has declined by >50% (confirmed), then study drug should be withheld and the investigator should contact the study medical monitor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding factors (e.g., background therapy, other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained.

8.7.7.1. Proximal Renal Tubule Dysfunctions (PRTD)

PRTD is defined as:

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

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

- Glycosuria (≥250 mg/dL) in a non-diabetic;
- Low serum potassium (<3 mEq/L);
- Low serum bicarbonate (<19 mEq/L).

Participants meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks of diagnosis. A urinalysis should also be performed at the time of the confirmatory assessment. If PRTD is confirmed participants should have study drug withheld and the investigator should contact the Study medical monitor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding factors (e.g., NRTI backbone, other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If study drug is reinitiated, it should have been withheld for no more than 4 weeks.

8.7.7.2. Proteinuria

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

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g, or >34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 μmol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study medical monitor should be contacted immediately. Agreement on further management should be agreed between the investigator and medical monitor.

8.7.8. QTc Prolongation

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

8.7.9. Injection Site Reactions (ISRs)

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

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

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

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

8.7.10. Allergic reaction

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

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

8.7.11. Abacavir Hypersensitivity Reaction (ABC HSR)

This section applies to participants who discontinue LA treatment and enter LTFU and are administered a regimen containing ABC.

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

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

0.8% (4/515) and 3.1% (6/192) of participants who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively.

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

8.7.11.1. Essential Participant Information

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

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

8.7.11.2. Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH E2A, 1994 definitions of seriousness listed in Section 12.4.2 then, in addition to reporting the case as an SAE, the ABC HSR eCRF should also be

completed within one week of the onset of the hypersensitivity reaction. Clinically suspected cases of HSR to ABC that do not meet criteria as an SAE can be recorded as an AE.

8.7.12. Rash Without ABC HSR Symptoms

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

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

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

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

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

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

CAB is an analogue of DTG and mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first 10 weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. No instances of serious skin reaction, including SJS, TEN and erythema multiforme, have been reported for DTG in clinical trials. For further characterization of HSR and rash observed with DTG-containing ART, please see the current version of the IB [GlaxoSmithKline Document Number RH2009/00003/07].

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

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

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

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

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings – see Section 12.3, Appendix 3).

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

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

Any 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.

8.8. Pharmacokinetics

Plasma samples for determination of CAB and RPV concentrations will be collected at Day 1, Month 12 and Withdrawal visits of the study. For participants receiving oral DTG + RPV, plasma samples for determination of DTG and RPV concentrations will be collected at the Withdrawal visit of the study. Additional samples will be collected for storage during the LTFU Phase (blood and plasma). Samples (blood and plasma) for determination of RPV concentrations will be protected from light at all times, from sampling collection through analysis.

8.8.1. PK Sample Collection

Blood samples for evaluation of CAB (2 mL each), RPV (2 mL each) and DTG (2 mL each) plasma PK concentrations will be collected from Q2M and oral DTG + RPV study participants as described in Table 5.

For participants transitioning from the LATTE study and receiving the CAB LA + RPV LA Q2M regimen at Day 1, PK samples should be collected within the window of 20-28 hours after the last oral dose of CAB + RPV was taken the day prior to the clinic visit. Participants will take their final dose of oral CAB + RPV in the clinic at Day 1 after the pre-dose PK sample.

These participants will be expected to complete a PK dosing diary card noting the date and time of the last three oral doses of IP prior to the scheduled clinic visits at Day 1. The information from the diary card and the actual date and time of the PK samples will be recorded in the eCRF. Additionally, dosing information on the clinic day, including dosing and the actual date and time of the PK samples, must be recorded on the eCRF.

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

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

Table 5 CAB and RPV Plasma Pharmacokinetic Sample Schedule

Participants receiving CAB LA + RPV LA **Q2M** injections	CAB and RPV	PK samples for storage only: Pre-dose: Day 1, Month 12, and Withdrawal LTFU Period (off-drug; storage sample) Months 1, 3, 6, 9, and 12
Participants receiving oral **DTG + RPV once daily**	DTG and RPV	PK samples for storage only: Withdrawal

PK window collection: All scheduled PK samples should be collected on the Day of the corresponding visit. Pre-dose samples will be taken prior to performing dosing within the clinic. Pre-dose sample collection at Day 1 (for participants transitioning from the LATTE study to Q2M dosing) should be collected 20 to 28 hours after the last oral dose of CAB and RPV was taken.

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

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

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

8.8.2. Rationale for PK Sampling Strategy

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

8.8.3. Sample Analysis

8.8.3.1. CAB and DTG Sample Analysis

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

Once the plasma has been analyzed for CAB and DTG, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK platform technology and science - drug metabolism and pharmacokinetics (PTS-DMPK), GSK protocol. No human deoxyribonucleic acid (DNA) analysis will be performed on these samples.

8.8.3.2. RPV Sample Analysis

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

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

8.9. Genetics

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

8.10. Viral Genotyping and Phenotyping

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

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

8.10.1. HIV-1 Polymerase Viral Genotyping and Phenotyping

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

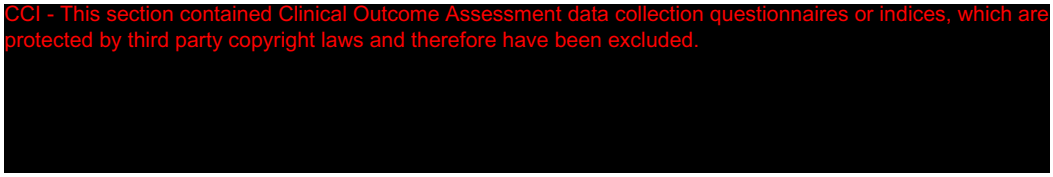
8.10.2. HIV-1 Exploratory Analysis

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

8.11. Value Evidence and Outcomes

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

The original HIVTSQ included 10 items and underwent two stages of psychometric validation (Woodcock, 2001; Woodcock 2006). Recently, the HIVTSQ was adapted to include injectable treatment for HIV following a qualitative study with HIV participants in five European countries. The adaptation of the HIVTSQ included two additional items related to the mode of administration (ie: long acting intramuscular injection). These are:

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

Psychometric analyses from three datasets (one from the UK, one from the USA, and one from the LATTE-2 trial) reveal that the addition of the two items in the original version of the HIVTSQ is suitable and does not reduce the overall validity of the questionnaire.

The current study will be using the HIVTSQs (status version) and the revised HIVTSQc (change version) of this recently developed HIVTSQ 12-item questionnaire. The HIVTSQ 12-item questionnaire retains the option of calculating the total score as if it only had the original 10 items (as the original 10 items are included in the HIVTSQ 12).

In addition, it allows for calculation of an 11-item scale score including the [redacted] item (item-[redacted]). The [redacted] item (item-[redacted] will be included in the questionnaire as a stand-alone item to evaluate potentially painful injectables. These measures will assess change in treatment satisfaction over time (in the same subjects) and compare current satisfaction with previous treatment satisfaction, from an earlier time point.

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

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

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

8.11.1. Value Evidence and Outcomes Endpoints (Secondary)

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

8.11.2. Value Evidence and Outcomes Endpoints (Exploratory)

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

8.12. Digital Reminder

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

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

9. DATA MANAGEMENT

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

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

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

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

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

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

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

10.2. Sample Size Determination

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

10.2.1. Sample Size Sensitivity

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

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

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

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

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

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

10.4. Statistical Analyses

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

Endpoint	Statistical Analysis Methods
	over time
Exploratory	Will be described in the reporting and analysis plan (RAP)

10.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	Descriptive summaries of the following safety endpoints will be produced: Incidence and severity of AEs and laboratory abnormalities over time Proportion of participants who discontinue treatment due to AEs over time Change from Baseline in laboratory parameters over time
Exploratory	Will be described in the reporting and analysis plan

10.4.2. Other Analyses

PK, viral resistance, health outcomes and digital assistance program analyses will be described in the reporting and analysis plan. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

10.5. Interim Analyses

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

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12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1. Appendix 1: Abbreviations and Trademarks

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
ABC/DTG/3TC	Abacavir/dolutegravir/lamivudine, TRIUMEQ
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core Antibody
Anti-HBs	Hepatitis B surface antibody
Anti-HbsAg	Antibodies against Hepatitis B surface Antigen
APAP	N-acetyl-para-aminophenol
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-τ)	Area under the concentration curve from 0 hours to the time of next dosing
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAB	Cabotegravir
CABG	Coronary artery bypass grafting
CAB LA	Cabotegravir long-acting
c/mL	Copies/milliliter
cART	Combination antiretroviral therapy
CHORUS	Clinical Health Outcomes Reporting and Utilization Service
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CDC	Centers for Disease Control and Prevention
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
CNS	Central Nervous System
CO_2	Carbon Dioxide
ConART	Concomitant Antiretroviral Therapy
COVID-19	Coronavirus Disease 2019
CPK	Serum creatine phosphokinase
CSR	Clinical Study Report
Ctrough	Trough Concentrations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences

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

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

PP	Per-protocol
PPL	Project Physician Leader
PPN	Pre- and Postnatal
PrEP	Pre-exposure prophylaxis
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSRAE	Possible suicidality-related adverse event
PT	Prothrombin Time
PTS-DMPK	Platform Technology and Science - Drug Metabolism and Pharmacokinetics
PTT	Partial Thromboplastin Time
PTCA	Percutaneous transluminal coronary angioplasty
PUD	Peptic Ulcer Disease
QTc	Corrected QT interval
Q2M	Every 2 months
Q8W	Every 8 weeks
Q4W	Every 4 weeks
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RPV	Rilpivirine, Edurant
RPV LA	Rilpivirine long-acting
RT	Reverse transcriptase
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
SMS	Short message service
SOC	Standard of Care
SPM	Study Procedures Manual
STR	Single tablet regimen
SVF	Suspected Virologic Failure
TDP	Torsade des Pointes
TEN	Toxic epidermal necrolysis
TMC278	Tibotec Medicinal Compound 278
UDP	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
VSLC	ViiV Safety and Labeling Committee
WBC	White blood cell
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of ViiV Healthcare
EPZICOM/KIVEXA
TIVICAY
TRIUMEQ
TRIZIVIR
ZIAGEN

Trademarks not owned by ViiV Healthcare
Edurant
Genosure
InForm
MedDRA
PhenoSense

12.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

12.2.1. Regulatory and Ethical Considerations

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

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

- This study will be conducted in accordance with the protocol and with:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.2.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.2.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

12.2.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized

personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

12.2.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

12.2.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.2.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

12.2.8. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- If ViiV/GSK determines such action is needed, ViiV/GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, ViiV/GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and ViiV/GSK Standard Operating Procedures.
- If the study is suspended or prematurely discontinued for safety reasons, ViiV/GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. ViiV/GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

12.2.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

12.3. Appendix 3: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017

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

12.3.1. Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

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

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
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.

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.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

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

Endocrine and Metabolic

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

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

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

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

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

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO BMI z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO BMI z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*	Same as for **Injection Site Erythema or Redness**, *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness**, *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness**, *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN with other signs and symptoms of hepatotoxicity.	≥ 5.0 x ULN with life-threatening consequences (e.g., signs and symptoms of liver failure).
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ 7 days of age	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ 7 days of age	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] **or eGFR, Low** **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Reference

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [March 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

12.4.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

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

12.4.2. Definition of SAE

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

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

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

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

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

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

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

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

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

12.4.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

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

Follow-up of AE and SAE

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

12.4.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool 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, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

12.5.1. Definitions

12.5.1.1. Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

12.5.1.1.1. Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.5.2. Contraception Guidance:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 7.

Table 7 Highly Effective Contraceptive Methods

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

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

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

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

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed as per the study Time and Events Table.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing will be performed and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert]

12.5.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 4 (Section 12.4). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will discontinue study intervention or be withdrawn from the study

12.6. Appendix 6: Genetics Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate a relationship between genetic variants and:

- Response to medicine, including CAB + RPV (LA and oral), DTG + RPV (oral) or any concomitant medicines;
- HIV-1 susceptibility, severity and progression and related conditions.

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a RAP prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any participant who is enrolled in the clinical study can participate in genetic research. Any participant who has received an allogeneic bone marrow transplant must be excluded from genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no a priori hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the participant has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the participant by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last participant completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Participants can request their sample to be destroyed at any time.

Informed Consent

Participants who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Participant Withdrawal from Study

If a participant who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the participant will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample.

If a participant withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by ViiV/GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a participant withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.

- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the participant does not meet the entry criteria for participation in the study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Participant's Genetic Data

ViiV/GSK may summarize the genetic research results in the CSR, or separately, and may publish the results in scientific journals.

ViiV/GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.7. Appendix 7: Liver Safety: Study intervention Restart or Rechallenge Guidelines

12.7.1. VSLC Guidelines for Drug Restart or Rechallenge after stop for Liver criteria

Drug Rechallenge refers to resuming study intervention following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI (see Drug Rechallenge Background below) this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favorable (Table 8, Figure 4).

Drug Restart refers to resuming study intervention following liver events meeting stopping criteria **in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis)**. Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury. (Table 9; Figure 5).

As this determination can be difficult, for the purpose of these guidelines, cases should be treated as rechallenges if there is any reasonable likelihood that the liver event is related to study drug. Restarts should be limited to cases in which there is clear evidence that the underlying cause of the liver event is not related to study drug.

DRUG RECHALLENGE

Background: Following drug-induced liver injury, drug rechallenge is associated with a 13% mortality across all drugs in prospective studies [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- participant currently exhibits severe liver injury defined by: ALT≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- evidence of drug-related nonclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

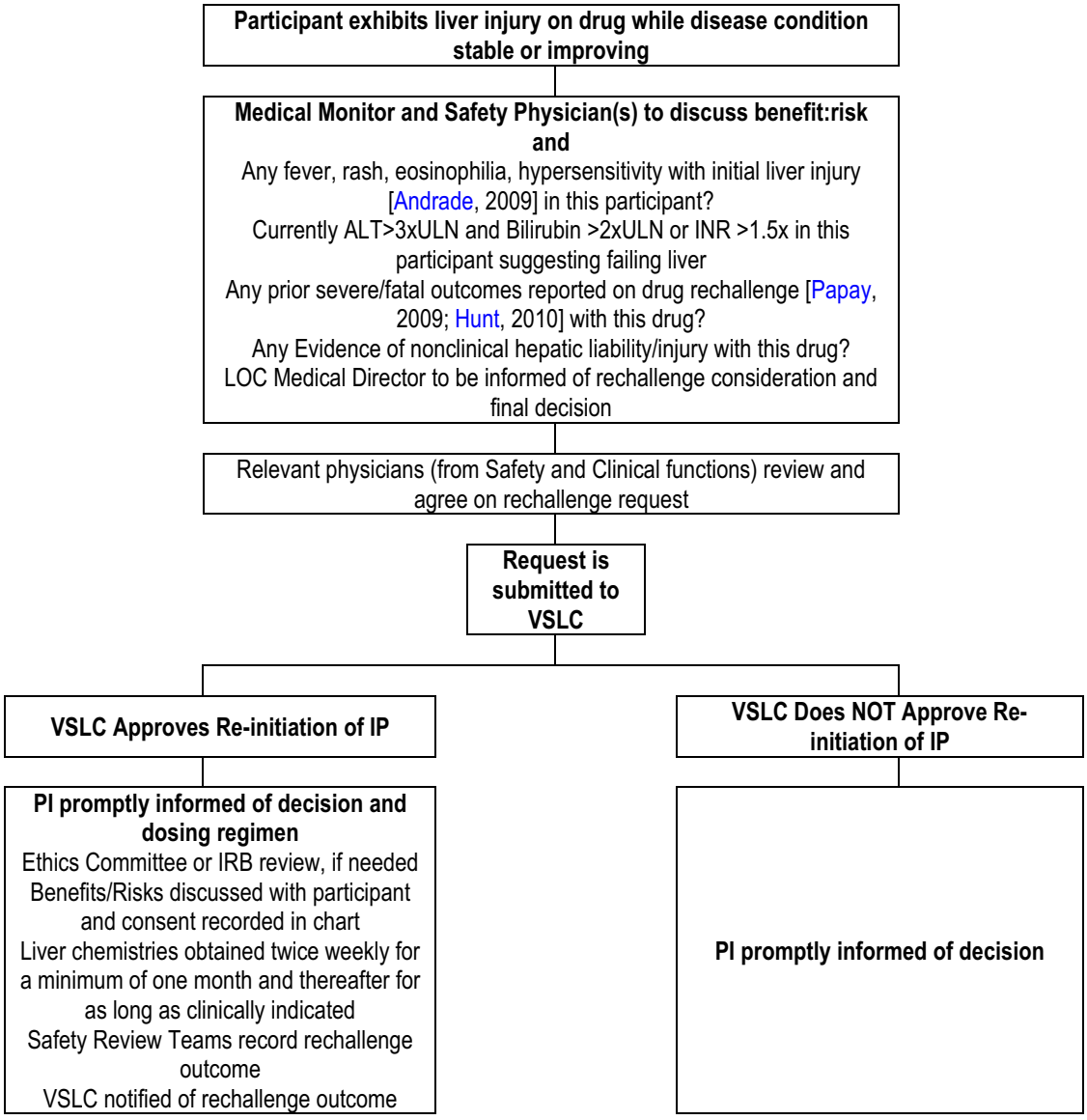
12.7.2. VSLC Decision Process for Drug Rechallenge Approval or Disapproval

- Principal Investigator (PI) requests consideration of drug rechallenge for a participant receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting participant stopping criteria in relation to DILI, with no alternative treatment
- By definition treatment naïve participants will only be considered for rechallenge if they were infected with a multi-resistant virus.
- Medical Monitor and Global Clinical Safety and Pharmacovigilance (GCSP) Physician review the participant's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and complete checklist (Table 8).
- The local operating company (LOC) medical directors (ViiV and/or GSK where applicable) should be informed that study drug rechallenge is under consideration and of the final decision, whether or not to proceed.
- The Medical Monitor and GCSP Physician are accountable to review and agree on the following prior to preparing request for rechallenge documentation for presentation to VSLC:
  - Compelling benefit of the investigational product (IP) for this participant and no alternative therapy
    - ***must present source data defining the participant's current resistance profile with documented evidence of extensive drug resistance and previous drug history***
- Relative benefit-risk of drug rechallenge, with consideration of the following high risk factors:
  - Initial liver injury event included: fever, rash, eosinophilia, or bilirubin ≥2xULN (or direct bilirubin >35% of total, if available)
  - Participant currently exhibits severe liver injury defined by: ALT >3xULN, bilirubin >2xULN (direct bilirubin >35% of total, if available), or INR>1.5
  - SAE or fatality has earlier been observed with IP rechallenge
  - IP is associated with known nonclinical hepatic liability/ injury
- Relevant physicians (listed below) must review and agree on action to be taken regarding request for drug rechallenge:
  - Safety Review Team Leader, Safety Development Leader, or Senior Safety Physician
  - Medicines Development Leader (MDL) and Project Physician Leader (PPL)
- Request is taken to full VSLC for final decision

Table 8 Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)

	Yes	No
Compelling benefit of IP for this participant and no alternative therapy. **Provide brief explanation**:		
Relative benefit-risk favorable for drug rechallenge, after considering the **following high risk factors**:		
Initial liver injury event included:		
fever, rash, eosinophilia, or hypersensitivity		
bilirubin≥2xULN (direct bilirubin >35% of total)		
Participant currently exhibits ALT >3xULN, bilirubin >2xULN (direct bilirubin >35% of total, if available), or INR>1.5		
SAE or fatality has earlier been observed with IP rechallenge If yes, please provide brief explanation:		
IP associated with known nonclinical hepatic liability/ injury		
Source data defining the participant's current resistance profile		
Previous drug history		

Figure 4 VSLC process for drug rechallenge approval or disapproval



DRUG RESTART

"Drug restart" can be approved by the VSLC for **transient, defined non-drug-induced** liver injury if no evidence of:

- immunoallergic injury /HLA association with injury
- alcoholic hepatitis

Study drug must be held while labs and evaluation are completed to assess diagnosis.

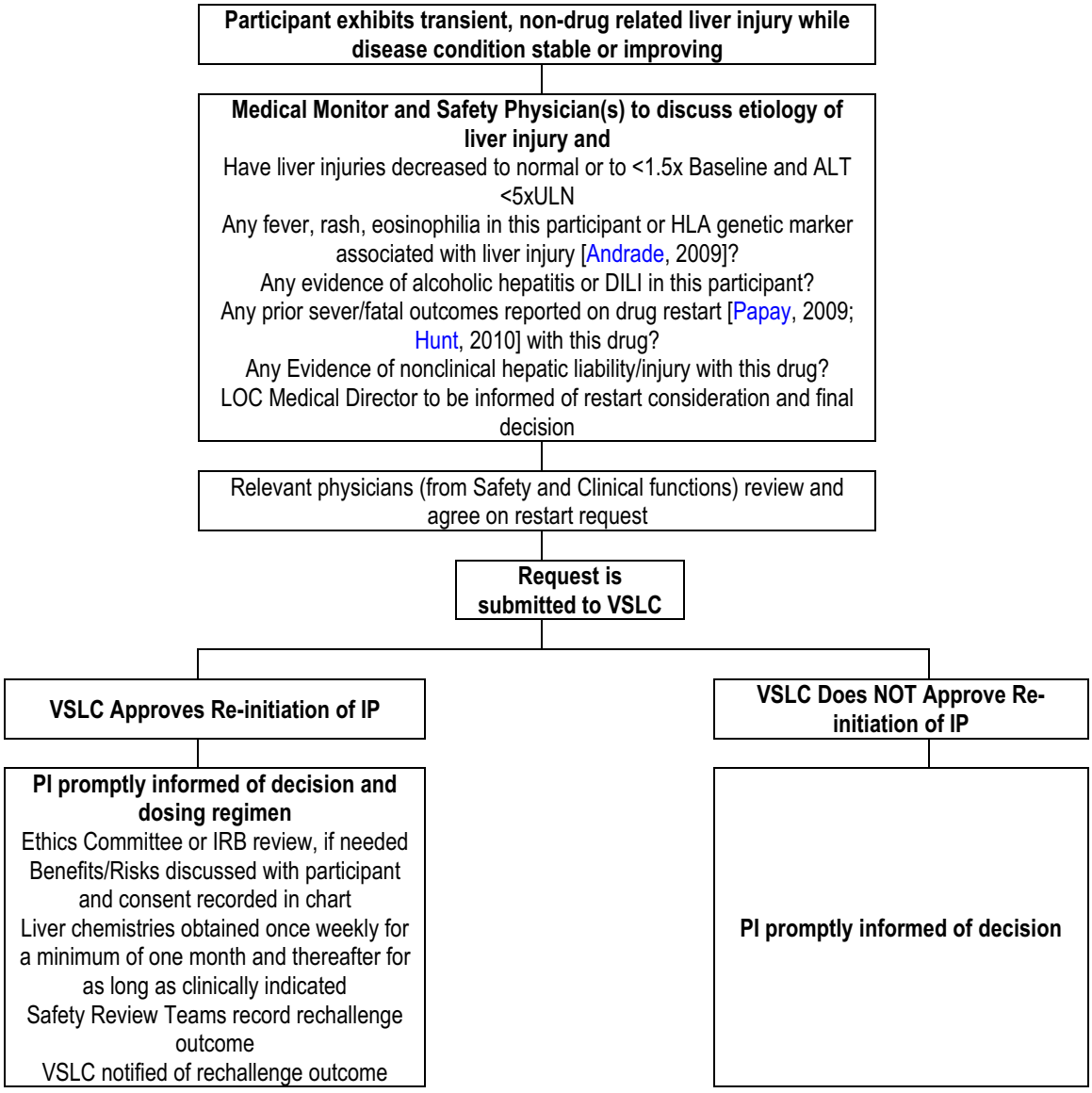
12.7.3. VSLC Decision Process for Drug Restart Approval or Disapproval

- Principal Investigator (PI) requests consideration of drug re-initiation for a participant stable or improving on IP, who exhibits liver chemistry elevation meeting participant stopping criteria, which is transient, non-drug-related, and liver chemistries have improved to normal or are within 1.5x baseline and ALT< 5xULN.
- GSK Medical Monitor and GCSP Physician to review the participant's diagnosis restart risk factors (Hepatotoxicity Panel consultation is available) and complete checklist (Table 9).
  - ***must present source data defining the participant's current resistance profile with documented evidence of extensive drug resistance and previous drug history***.
- The local operating company (LOC) medical director should be informed that study drug restart is under consideration and of the final decision, whether or not to proceed.
- Relevant physicians (listed below) must review and agree on action to be taken regarding request for drug restart:
- Safety Review Team Leader, Safety Development Leader, or Senior Safety Physician
- MDL and PPL
- Request is taken to VSLC for final decision

Table 9 Checklist for Phase IIb drug restart after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, congestive heart failure (CHF), acute viral hepatitis), and improvement of liver chemistry to normal or ≤1.5x baseline & ALT<5xULN

	Yes	No
Is participant stable or improving on IP?		
Do not restart if the **following risk factors at initial liver injury**:		
fever, rash, eosinophilia, or hypersensitivity		
drug-induced liver injury		
alcoholic hepatitis (AST>ALT, typically <10xULN)		
IP has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		
Source data defining the participant's current resistance profile		
Previous drug history		

Figure 5 VSLC process for drug restart approval or disapproval



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

12.7.4.1. Medical Monitor and GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's rechallenge (or restart) decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.
- The Safety Review Team must record rechallenge (or restart) outcomes and the GCSP Physician must send these to the VSLC (see template below).
- All severe reactions (rechallenge associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities which occur following a drug rechallenge (or restart) must be immediately reported to Line Management including, VSLC

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

12.7.4.2. PI Actions:

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

Drug Rechallenge or Drug Restart Outcomes Table Template

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

Drug Rechallenge/Restart Outcomes Table – Update with each event

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

Rechallenge/restart safety outcomes:

0 = no liver chemistry elevation

1 = recurrent liver chemistry elevation not meeting participant stopping criteria

2 = recurrent liver chemistry elevation meeting participant stopping criteria

3 = serious adverse event

4 = fatality

12.8. Appendix 8: CDC Classification for HIV-1 Infection (2014)

Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte should only be considered if the count is missing.

HIV infection, stage 0

Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

HIV infection, stage 1

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of ≥500 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

HIV infection, stage 2

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

HIV infection, stage 3 (AIDS)

- Laboratory confirmation of HIV infection, and
    - CD4+ T-lymphocyte count of <200 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or
    - Documentation of an AIDS-defining condition (see below).

Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

HIV infection, stage unknown

- Laboratory confirmation of HIV infection, and
    - No information on CD4+ T-lymphocyte count or percentage, and
    - No information on presence of AIDS-defining conditions.

Stage-3-defining opportunistic illnesses in HIV infection

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of oesophagus
- Cervical cancer, invasive

- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or oesophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV.

Reference

CDC. Revised Surveillance Case Definition for HIV Infection – United States, 2014. MMWR 2014; 63 (RR-03);1-10.

12.9. Appendix 9: Country-specific requirements

12.9.1. Study Duration

In this study, the intention to provide access to CAB LA + RPV LA Q2M or DTG + RPV based on participants elected assignment until the regimen receives local (by country) Regulatory approval, and becomes commercially available. Therefore, the duration of the study will vary from country to country and is dependent on the recruitment time for the study and the time taken to achieve local approval for marketing. During this time, participants will be monitored at minimum every 2 months to ensure they continue to derive clinical benefit from CAB LA + RPV LA and DTG + RPV.

12.10. Appendix 10: COVID-19 Pandemic and Clinical Trial Continuity

Background

The COVID-19 pandemic presents significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual participants ability to attend clinic visits. In some places, medical visits are occurring, and in others, research clinics are operating with only emergency staff.

Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to ensure that there are no gaps in HIV-1 treatment for participants enrolled in this clinical study, through continuous access to antiretroviral therapy.

In order to maintain the scientific integrity of the study, and adhere to updated guidance from regulators, procedures have also been put into place to ensure that the actions taken to mitigate against any impact of COVID-19 are well documented in the trial database.

A "Memo to Investigators" was issued on March 18th, 2020 and served as a record of approved emergency actions being taken within this clinical trial to manage issues related to COVID-19. That memo continues to serve as record of approved actions which can be fully implemented by Investigators, in advance of this protocol guidance. This appendix will remain consistent with the guidance provided within the "Memo to Investigators" and will also serve to provide additional protocol documentation requirements and procedures.

This appendix outlines the measures which are approved for implementation within this clinical trial, to protect patient safety and to ensure the integrity of the clinical trial, as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Independent Review Boards/Independent Ethics Committees and National Competent Authorities, as necessary.

This appendix **does not** apply to participant management issues that are unrelated to a specific, and documented, impact from COVID-19.

12.10.1. Changes to Study Visits and Study Procedures

- Where site staff resource is constrained due to COVID-19, IM dosing visits may proceed with limited or no other protocol-defined assessments (e.g. lab tests, questionnaires, etc.). If lab tests will be missed for more than one consecutive visit, the medical monitor must be contacted, to provide guidance for safety monitoring.
- For WOCBP, point of care pregnancy testing should be performed, prior to IM dosing.
- If central laboratory testing cannot be performed at a particular visit, and monitoring for safety is required, tests may be performed at an appropriately

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

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

12.10.2. Changes to Informed Consent

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

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

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

12.10.3. Permissible Use of Antiretroviral Therapy

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

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

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

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

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

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

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

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

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

Oral bridging with Standard of Care Antiretroviral Therapy (SOC ART)

For participants impacted by COVID-19, where the participant is unable to receive IM injections, and oral CAB + RPV is not available for use, oral bridging with any commercially available, guideline-recommended, SOC ART regimen is permitted. The start date of oral bridging should be within the dosing window for the missed IM dosing visit. Please reach out to your study medical monitor for approval of SOC ART as oral bridging, in order to document the use of commercially available SOC ART within the study.

Participants who use oral SOC ART as short-term oral bridging as a result of COVID-19 will not be considered formally withdrawn insofar as they wish to continue on the study. Individuals who bridge with SOC ART will be permitted to return to IM dosing, on study, once the COVID-19 conditions permit resumption of site activities.

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

12.10.4. Direct-To-Patient (DTP) Shipment of Oral Study IP

If a participant is unable to travel to the clinic, either to receive IM injections or to be dispensed oral bridging, sites are encouraged to consider DTP shipments of drug, from the site, to the participant, to ensure access to medicines.

- If the study site is considering DTP shipment of oral CAB + RPV investigational product (IP), the site must first verify if DTP IP dispensing by investigators/hospital pharmacies is locally permitted and whether it requires regulatory and/or local ethics pre-approval, or post-hoc notification.
- The study participant should express his/her agreement for DTP shipment and the sharing of their personal information with any third-party couriers (as applicable), in accordance with local requirements. This agreement should be documented in source records.
- Oral CAB + RPV IP can be shipped at ambient temperatures via ground transport without a temperature monitoring device, with low risk of temperature excursions. Sites are encouraged to use discretion in determining the need for in-transit temperature monitoring based on the labelled storage requirements and the planned mode of transport and apply this as appropriate. Shipment of oral CAB + RPV via air courier continues to require appropriate temperature monitoring. For shipment conditions of oral medications other than oral CAB + RPV, please consult the product labelling.
- In all cases IP accountability must be maintained, and all DTP dispensing documentation should be reflected in source records and dispensing logs per GCP.

- Please refer to your CRA or local study manager for support with the DTP process, ensuring reference to current sponsor guidance and arrangement of a courier that can support shipment of IMP directly to participants.

12.10.5. COVID-19 Experimental Agents

If any treatments for COVID-19 are planned for a study participant, please consult with the study medical monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate.

12.10.6. COVID-19 Specific Data Capture

12.10.6.1. Capturing COVID-19 Specific Protocol Deviations

In order to summarise the impact of COVID-19 in a systematic way and in line with regulatory authorities' recommendations, any study-level impact around COVID-19 will be documented as a protocol deviation. This will include the permissible actions summarized in this Appendix, which are taken to protect patient safety, including the use of CAB + RPV or SOC ART as oral bridging as well as missed visits and assessments as a result of logistical challenges resulting from COVID-19.

Although the conduct of remote visits and the continuity of antiretroviral therapy, via oral bridging, are being utilized to protect patient safety, these events fall outside of the intent of the original protocol design, may have an impact on data interpretation, and thus will be characterized as protocol deviations for the purposes of data summary and analysis.

Any protocol deviations resulting from COVID-19 will be clearly identified as such within the protocol deviation description and summarised separately.

Please refer to your study procedure manual for specific details on capturing protocol deviations as a result of COVID-19.

12.10.6.2. Capturing COVID-19 Specific AEs and SAEs

It is important for the study team to describe COVID-19 related adverse events/serious adverse and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines.

2. When an in-person clinic visit is not possible, please conduct a remote telehealth visit to assess for, and document any AEs/SAEs.

3. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released March 20, 2020, represents a time point for standardized collection. We recognize definitions are likely to continue to evolve. When reporting both serious and non- serious adverse events (related to COVID-19 infection, investigators should use the following Verbatim terms:
    a) Suspected COVID-19 infection; or
    b) Probable COVID-19 infection; or
    c) Confirmed COVID-19 infection

4. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation.

5. A new COVID-19 infection Case Report Form will be added to the eCRF to collect additional details about the reported COVID-19 AE or SAE data. It is important to collect the correct information from each participant reporting a COVID-19 AE or SAE. Therefore, please use the CRF templates to help you collect this information, once available.

WHO Case Definition - March 20, 2020 Version (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)):

Suspected case:

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

B. A patient with any acute respiratory illness AND in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive (Inconclusive being the result of the test reported by the laboratory).

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Covid-19 Contact:

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR
4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

12.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1, 22-Jun-2018

Overall Rationale for the Amendment: This amendment was completed to clarify procedures, adjust exclusion criteria, add missing risk assessment language and to clean up minor grammatical errors.

Section # and Name	Description of Change	Brief Rationale
Title page	Update of abbreviated study title	Updated to match eTrack
Section 1.1 Synopsis	Update of abbreviated study title	Updated to match title page
Section 1.3 Schedule of Activities	Clarification of procedures in SoA	Updated to provide clarity, removed completion of ISR diaries and match Time and Events tables in main protocol body.
Section 2.3.1 Risk Assessment	Addition of DTG + RPV risk assessment	Updated to add in most up to date safety and risk information
Section 5.2 Exclusion Criteria	Removal of Exclusion Criteria #7	Participants who are diagnosed with syphilis can enrol in study and be treated.
Section 8.1 Time and Events Table	Update of procedures	Updated to provide clarity and remove completion of ISR diaries.
Section 8.8 Pharmacokinetics	Addition of DTG PK storage sample information	Left out in error in original document
Section 11 References	Updated DTG IB reference to most up to date version	Update to ensure most up to date DTG safety and efficacy data is utilized.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized