TITLE PAGE

Protocol Title: A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics and Tolerability of Cabotegravir and Rilpivirine Long-Acting Injections Following Intramuscular Administration in the Vastus Lateralis Muscle of Healthy Adult Participants

Protocol Number: 208832/01

Compound Number GSK1265744, GSK1329758

Study Phase: Phase 1

Short Title: Cabotegravir LA and Rilpivirine LA Thigh PK Study

ViiV Healthcare group of companies

US IND Sponsor Name and Legal Registered Address:

ViiV Healthcare Company
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: + 1 919 438 2100

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

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

Regulatory Agency Identifying Number(s):

IND: 109,678

Approval Date: 13-AUG-2020

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 1	*13-AUG-2020*	*2018N357118_01*
Original Protocol	*02-MAR-2020*	*2018N357118_00*

Amendment 1: 13-AUG-2020

Overall Rationale for the Amendment:

Revisions were made to the study eligibility criteria and safety assessments to further mitigate the potential risks for study conduct during the COVID-19 pandemic.

Section # and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Activities (SOA)	SOA revised to include SARS-CoV-2 testing at Screening and on admission to the Phase I unit prior to the oral lead-in phase	To mitigate risk to study conduct during the COVID-19 pandemic
5.1 Inclusion Criteria	Participant age range revised so that no participants >50 years of age are included	To mitigate risk to study conduct during the COVID-19 pandemic
5.1 Inclusion Criteria	Included a new criterion for participants to have two consecutive negative tests for SARS-CoV-2 at Screening and on admission	To mitigate risk to study conduct during the COVID-19 pandemic
5.2 Exclusion Criteria	Included two new criteria excluding participants having signs and symptoms suggestive of COVID-19 and participants who had contact with a known COVID-19 positive person/s within 14 days prior to admission	To mitigate risk to study conduct during the COVID-19 pandemic
8.1.4. Clinical Safety Laboratory Assessments	Information on screening for SARS-Cov-2 included	To mitigate risk to study conduct during the COVID-19 pandemic
8.4 Pharmacokinetics	One additional PK sampling timepoint added (Day 1 12h) and modification of sampling window for Day 1 8h and Day 2 PK during OLI Phase	Since participants remain at the site overnight on Day 1 during OLI, additional PK timepoints was added to improve precision of PK parameter estimation
11.8. Appendix 8: Permissible	Investigator(s) should utilise WHO Case Definitions to classify	To mitigate risk to study conduct during the COVID-19 pandemic

Section # and Name	**Description of Change**	**Brief Rationale**
Procedures during the COVID-19 Pandemic 12. References	COVID-19 cases [World Health Organisation, 2020]. WHO reference included.	
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics and Tolerability of Cabotegravir and Rilpivirine Long-Acting Injections Following Intramuscular Administration in the *Vastus Lateralis* Muscle of Healthy Adult Participants

Short Title: Cabotegravir LA and Rilpivirine LA Thigh PK Study

Rationale: The objective of this study is to evaluate the pharmacokinetics, tolerability, and safety of cabotegravir (CAB) long acting (LA) + rilpivirine (RPV) LA administered concomitantly as two separate IM injections in the *vastus lateralis* muscle of adult healthy participants. Data from this study will be used to inform the feasibility of administering CAB LA + RPV LA in the *vastus lateralis* muscle in HIV-infected children < 12 years of age and adult populations.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To describe the PK profiles of CAB and RPV following a single intramuscular injection each of CAB LA + RPV LA administered to the lateral thigh muscle in adult healthy participants	• Maximum observed concentration (Cmax) and time of maximum observed concentration (tmax) in plasma • Area under the concentration – time curve from time zero to last quantifiable time point (AUC(0-t)) through the follow-up phase • Area under the concentration – time curve from time zero to infinity (AUC0-∞) • Apparent terminal phase half-life (t½) and absorption rate constant (KALA))
Safety	
• To assess safety and tolerability of CAB and RPV following repeated oral dose and single intramuscular injection in the lateral thigh of healthy participants	• Safety and tolerability parameters including adverse events (AEs), clinical laboratory tests, electrocardiogram (ECG), and vital sign assessments

Overall Design:

This is a Phase 1, open label study conducted in healthy participants to assess the PK of CAB and RPV in plasma following a single 600 mg (1 x 3 mL) and a 900 mg (1 x 3 mL) injection each, respectively, administered IM to separate *vastus lateralis* muscles on each leg.

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 participant's ability to attend clinic visits. Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to allow flexibility to allow conduct of the study.

Number of Participants:

Approximately 15 adult healthy participants will be dosed with injectable study interventions. If participants prematurely discontinue the study, for any other reason, other than an AE, additional replacement participants may be enrolled at the discretion of the Sponsor in consultation with the investigator.
Approximately 30% of female participants will be enrolled.

Intervention Groups and Duration:

The study will consist of

- 30-day screening period
- 28-day oral lead-in (OLI) phase at a CAB dose of 30 mg and RPV dose of 25 mg once a day with a meal
- 10 – 14 days washout period
- CAB and RPV injection, administered IM: 600 mg (1 x 3 mL) CAB on left and a 900 mg (1 x 3 mL) RPV injection on right *vastus lateralis* muscle
- Sparse PK sampling for up to 29 days in OLI and serial PK sampling for up to 4 weeks after the injection, per SoA. Participants will return for safety assessments and additional PK sampling at Week 8, 12, 24, 36, and 52 post last injection during the follow-up phase.

Data Monitoring or other Committee: No

1.2. Schema


Screening
Oral Lead-In Day 1
Oral Lead-in Day 28
Injection Day 1
Week 4
Week 8
Week 12
Week 24
Week 36
Week 52
Within 30 days
Oral CAB 30mg + RPV 25mg daily for 28 days
10-14 Days Wash-out
PK collection at Pre-dose, 2h on Day 1 and Days 2, 4, 5, 7/8, 10, 15, 17, 22, and 28 (Week 4) post injection
Follow- Up Phase: Week 8, 12, 24, 36, and 52 weeks post Injections
Injection Day 1:CAB LA 600mg IM (3mL) + RPV LA 900mg IM (3mL) Lateral thigh

1.3. Schedule of Activities (SoA)

The timing and number of planned study assessments, including as outlined in the SoA below, including safety and pharmacokinetic or other 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) and to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). Appendix 8 summarises permissible procedures during the COVID-19 pandemic (Section 11.8).

1.3.1. Screening and Oral Lead-in Phase

Study Period	**Screening[1]**		**Oral Lead-in[9]**			**Day 29**	**Early Withdrawal[9]**	**Washout Period**
			Dosing Days 1-28					
Visit Window	**Within 30 days of oral lead-in**	**Day -1**	**Day 1**	**Day 2**	**Day 14**	**Within 24 hours of the Day 28 last dose**	**EW**	**10 – 14 days**
Informed Consent	X							
Demographics	X							
Medical / Medication / Drug / Alcohol History	X							
Inclusion/Exclusion Criteria[2]	X		X					
Height, Weight, BMI	X							
Physical Exam	X		X					
Vital Signs[3]	X		X	X	X	X	X	
12-Lead ECG	X		X			X		
Drug / Alcohol Screen[3]	X		X					

Study Period	**Screening[1]**		**Oral Lead-in[9]**			**Day 29**	**Early Withdrawal[9]**	**Washout Period**
			Dosing Days 1-28					
Visit Window	**Within 30 days of oral lead-in**	**Day -1**	**Day 1**	**Day 2**	**Day 14**	**Within 24 hours of the Day 28 last dose**	**EW**	**10 – 14 days**
Pregnancy Test[3]	X		X		X	X		
Testing for SARS-CoV-2[4]	X	X						
Hepatitis B, Hepatitis C Screening	X							
HIV Test	X							
Urine Dipstick	X							
Hematology with differential; Clinical Chemistry Tests[3]	X		X	X	X	X	X	
Coagulation Tests	X							
Admit to clinic		X						
Dispense Oral lead-in IP			X					
Administer oral CAB + RPV[5]			X	X	X			
Dispense Medication Dosing Diary				X				
Drug accountability/ pill count/review drug diary				X	X	X		
Blood plasma PK sampling[6]			X	X	X	X	X	
AE Assessment[7]			X	X	X	X	X	
Concomitant Medication Review			X	X	X	X	X	
Genetic sample[8]			X					
Discharge from the clinic				X				

1. Screening may occur over more than one visit but within 30 days of the first dose of oral CAB and RPV in the oral lead in phase.

2. Eligibility criteria must be carefully assessed at the Screening visit and confirmed at the Day 1 Oral lead-in phase visit and re-confirmed prior to injection.
3. Prior to administering the first oral dose of CAB and RPV, study personnel must verify the following pre-dose assessments to be within normal limits prior to administration: vital signs, pregnancy test (negative; Females of Reproductive Potential (FRP) only. The results of the Drug/Alcohol screen, hematology with differential, and clinical chemistry tests on Day 1 are not required prior to administering the first oral doses of CAB and RPV but should be drawn prior to CAB and RPV administration.
4. Two consecutive approved molecular tests (PCR or antigen test) must be conducted on all study participants and separated by >48 hours. Following the second test for SARS-CoV-2, participants should be quarantined within the unit. Once the second test is negative, the participant can be released into the unit and follow Infection Control practices
5. Oral CAB and RPV dosing Days 1 to 28. Day 1, Day 2, and Day 14 doses should be administered in the clinic.
6. PK sampling – On Day 1 - 1h, 2h, 3h, 4h, 6h, 8h, and 12h, and Day 2 PK between 22 to 26 h post first oral dose. On Day 14 pre-dose samples. Day 29 PK should occur between 22 to 26 hours from the last dose on Day 28. Total of 20 PK samples (10 for CAB, 10 for RPV assay) will be collected during oral lead-in phase. Please refer to Section 8.4 for permitted PK window for OLI phase.
7. AE assessment will include a brief, symptom-directed physical exam as needed.
8. Genetic sample - collect the sample at the earliest convenient time after the first dose in the oral lead in phase on Day 1.
9. If a participant is withdrawn prior to receiving the CAB LA and/or RPV LA injection, a follow-up/withdrawal visit should be scheduled 10-14 days after the last oral dose of CAB and RPV.

1.3.2. CAB LA + RPV LA Injection Phase and Follow- up

Procedures	Injection Phase											Follow-up						
	Injection Day 1			Day 2	Day 4	Day 5	Day 7/8	Day 10	Day 15	Day 17	Day 22	Day 28 (Week 4)	Week 8	Week 12	Week 24	Week 36	Week 52	Withdrawal[1]
	Pre-dose[2]	1h	2h	24h	72h	96h	168h											
Permitted window for PK collection	Within 1 h prior to dosing	± 15 min	± 30 min	± 2 h	± 2 h	± 2 h	± 2 h	± 2 h	± 2 h	± 2 h	± 2 h	± 2 h	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	
Interim Medical/Medication/ Drug / Alcohol History[2]	X																	
Pregnancy Test	X											X	X	X	X	X	X	X
12-Lead ECG[2]	X		X			X											X	X
HIV Test	X														X		X	X
Hematology; Clinical Chemistry	X						X			X		X	X	X	X	X	X	X
Vital Signs[2]	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Administer CAB LA + RPV LA[2]	X																	
CCI		X[3]		X[3]	X[3]	X[3]	X[3]											
							X[3]											
Injection site reaction assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood plasma PK Sampling[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Participants who terminate before week 52 will be asked to return to the site for a withdrawal visit.

2. On Day 1, study personnel must verify the following pre-dose assessments to be within normal limits prior to injection: ECG, vital signs, pregnancy test (negative; FRP only), review AE assessment, and concomitant medications. If a clinical abnormality, clinically significant AE, or prohibited medication that precludes injection is observed/recorded, the medical monitor must be contacted for further instruction.
3. Participants will be asked to describe the comfort level with the injections received. CCI [redacted] CCI [redacted]
4. AE assessment will include a brief, symptom-directed physical exam as needed.
5. Total of 34 PK samples (17 each for CAB and RPV) will be collected through CAB LA + RPV LA Injection Phase and Follow-up.

2. INTRODUCTION

2.1. Study Rationale

Cabotegravir (CAB) is an integrase inhibitor being developed in combination with rilpivirine (RPV, TMC278), a non-nucleoside reverse transcriptase inhibitor, for the treatment of HIV. CAB is currently in Phase 3 development as monotherapy for the prevention of sexually-acquired HIV-1 infection. CAB and RPV are separately formulated as oral tablets for once daily administration and as long-acting (LA) aqueous suspensions for parenteral administration monthly or every 2-months. RPV 25mg oral tablets is approved as EDURANT in multiple countries, including the USA, Europe and Canada, for use in antiretroviral (ARV) treatment-naïve patients.

A two-drug long-acting, monthly antiretroviral regimen of CAB + RPV has demonstrated good efficacy, tolerability, and long-term safety in HIV-infected adults following oral and monthly and every 2-month IM dosing in the gluteus muscle for durations exceeding 3 years in Phase 2 and Phase 3 studies [LATTE, 2019; LATTE-2, 2018; ATLAS, 2019; FLAIR, 2019, ATLAS-2M, 2018]. Review and approval of the CAB + RPV regimen for treatment of HIV infection is ongoing.

Separate early Phase 1 studies of CAB LA and RPV LA evaluated PK and tolerability of single and repeat-dose injections in other anatomic locations including abdomen (subcutaneous) and IM administration in the ventrogluteal muscle (CAB), *gluteus maximus* muscle (RPV), and deltoid muscle (RPV) in healthy volunteers [HIV Therapy, 2013; International AIDS Society, 2013; RPV LA NATAP report, 2008]. Gluteal injections of CAB LA + RPV LA were progressed in late-stage studies given better participant tolerability to injections at this injection site with the anticipated injection dosing volume required to achieve desired exposures.

There remains considerable interest in exploring alternative injection sites either as an alternative rotational (e.g. gluteal injection fatigue) or chronic injection site (e.g. gluteal implants contraindicating injection or young pediatric populations without sufficient gluteal mass for injection). The *vastus lateralis* muscle in the thigh has been used as an injection location for other drugs (e.g. epinephrine, etc.) and is a common injection site in young children (e.g. vaccines). Moreover, self- or partner-injection of CAB LA + RPV LA in the thigh muscle may be explored in future studies pending favorable pharmacokinetics, safety, and tolerability of CAB LA + RPV LA thigh injections.

The objective of this study is to evaluate the pharmacokinetics, tolerability, and safety of CAB LA + RPV LA administered concomitantly as two separate IM injections in the *vastus lateralis* muscle of adult healthy participants. Data from this study will be used to inform the feasibility of administering CAB LA + RPV LA in the *vastus lateralis* muscle in HIV-infected children <12 years of age and adult populations.

2.2. Background

The treatment of HIV-1 infection has advanced since the first oral antiretroviral agent (AZT) was approved for the treatment of HIV-1 infected individuals in 1987. Newer

antiretrovirals are more potent, better tolerated and have enabled the formulation of multiple regimens that can provide viral suppression with a single tablet once daily.

Long acting injectable versions of drugs are being developed to enable therapy with infrequent dosing schedule. These therapeutic options hold great promise for future treatment and represent an emerging paradigm for the treatment of HIV infection. CAB is a potent integrase inhibitor that possesses attributes that allow formulation and delivery as a long-acting parenteral product. RPV is a diarylpyrimidine derivative and a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild type HIV-1 and select NNRTI-resistant mutants. A two-drug regimen with CAB LA plus RPV LA (CAB + RPV LA) offers many potential advantages over daily oral regimens including infrequent dosing that decreases the daily reminder to patients of their HIV status, better tolerability, less likely to develop viral resistance due to intermittent compliance with oral agents that can lead to sub-therapeutic concentration of antiretroviral medication and emergence of resistance, and improved adherence and overall treatment satisfaction in virologically suppressed patients. Results to date have demonstrated the efficacy of a two-drug regimen of CAB + RPV LA as maintenance therapy with several on-going Phase 2 and 3 studies including LATTE-2, ATLAS, FLAIR, and ATLAS 2M currently underway [ATLAS, 2019; FLAIR, 2019]

As of 18-Oct-2018, in the Phase 3 Study 201584, a total of 283 HIV-infected subjects have received CAB 30 mg once daily with RPV 25 mg once daily as oral lead-in (OLI) therapy prior to initiation of injections. Of these subjects, 278 have received CAB LA + RPV LA gluteal injections (dosed every 4 weeks, Q4W) during the Maintenance Phase of the study. In Phase 3 Study 201585, a total of 308 HIV-infected subjects entered the Maintenance Phase and received CAB 30 mg once daily and RPV 25 mg once daily as OLI therapy prior to initiation of gluteal injections. Of the 308 subjects who received OLI, 303 transitioned to receive CAB + RPV LA injections (dosed Q4W). Of the 308 subjects that entered the Maintenance Phase, 282 successfully completed and 26 subjects withdrew. A pooled analysis of the Phase 3 studies demonstrated that monthly injections with CAB + RPV LA were non-inferior to daily oral antiretroviral therapy for the key virologic endpoints at week 48. Low confirmed virologic failure was seen across both treatment arms. Injection site reactions in the LA arm were mainly Grade 1 or 2 but with few associated discontinuations.

To date, Phase 2 and Phase 3 studies of CAB LA + RPV LA have utilized the *gluteus medius* injection site in HIV-1 patients. This study aims to evaluate alternate injection site of thigh muscles for CAB LA + RPV LA administered in injection per each thigh muscle, at the same visit.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse effects of CAB and RPV may be found in the [CAB IB 2019; GlaxoSmithKline Document Number RH2009/00003/09; RPV IB, 2019].

2.3.1. Risk Assessment

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 >3100 participants) have developed transaminitis (elevated liver transaminases characterized by predominant alanine aminotransferase (ALT) elevation). In most participants, transient transaminitis was explained by acute viral hepatitis infection (. 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 participants with suspected DILI identified to date were receiving oral CAB.	• Exclusion criteria as described in Section 5.2 will prohibit participation with significant liver impairment based on screening liver chemistry including transaminases (ALT and Aspartate aminotransferase [AST]) as well on prior medical history. • A 4-week oral lead-in Phase is being implemented in this study, where all participants will receive oral CAB prior to the administration of IM CAB to assess individual safety and tolerability Liver transaminases (ALT and AST) will be monitored throughout this study (refer to Schedule of Activities) and the liver chemistry stopping criteria will be adopted as described in Section 7.1.1 of this protocol. • All instances of liver transaminase elevations of Grade 2 and above will be followed to resolution. Participants withdrawn from the study due to meeting liver chemistry stopping criteria will be regularly monitored both clinically and using liver chemistries to determine progress towards resolution of the liver event.
Effects in late stage pregnancy seen in non-clinical studies	In animal reproduction studies, CAB when administered to rats at > 30 times the systemic exposure at the maximum recommended oral human dose (MRHD) of 30 mg during organogenesis through delivery, had adverse effects on labor and delivery that may be related to a delay in the onset of parturition, resulting in increased fetal mortality (stillbirths) and neonatal deaths immediately after birth. The clinical significance of these finding in humans is unknown.	• As a routine precaution, pregnant women are excluded from participation in this study 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 if pregnancy is identified.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential effects in women exposed to dolutegravir during conception and early pregnancy	A preliminary analysis of an ongoing birth outcome surveillance study in Botswana involving women exposed to dolutegravir (DTG) a different molecule in the same integrase class of medications as CAB, identified four cases (as of May 2018) of neural tube defects in 426 infants born to mothers who were exposed to DTG-containing regimens from the time of conception. In the same study, no infant born to a woman who started DTG during pregnancy had a neural tube defect, out of 2,824 women. A causal relationship of these events to the use of DTG has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As neural tube defects occur within the first 4 weeks of fetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to DTG at the time of conception and in early pregnancy. The clinical relevance of either of these findings in relation to CAB use is unknown	• As a routine precaution, pregnant women are excluded from participation in clinical trials of CAB at this time and females of reproductive potential (FRP) are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies after exposure to CAB and RPV LA. • Females of reproductive potential also undergo regular pregnancy testing throughout study conduct to enable early discontinuation of study drugs once pregnancy is identified. However, it should be noted that CAB concentration could remain for prolonged periods despite discontinuation of CAB LA.
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for CAB, CAB LA, RPV and RPV LA, refer to Section 6.4.	• All participants will be informed of prohibited medications throughout the study and updates provided as needed via the informed consent.
Injection Site Reactions (ISR)	There are extensive safety and tolerability data, including ISRs following IM administration of CAB LA and RPV LA. Please refer to each IB for additional information [CAB IB GlaxoSmithKline Document Number RH2009/00003/09, RPV IB, 2019]	• 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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 mild). Severe skin and hypersensitivity reactions have been reported during the post-marketing experience with oral RPV-containing regimens, , including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). 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 developing a Grade 3 or 4 rash should discontinue study drugs 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 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. In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine, levocetirizine, loratadine, diphenhydramine, topical corticosteroids, or antipruritic agents is permitted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that CAB LA and/or RPV LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher than expected concentrations of CAB and/or 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.	• 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. • 2-hour post dose PK samples will be for determination of CAB and RPV concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes.
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 CAB and RPV will be minimized by the use of a 4-week oral lead-in of oral CAB/RPV to determine individual safety and tolerability prior to the introduction of IM CAB. • Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study. Results from these assessments may aid early detection of HSR. • Oral CAB will be withdrawn immediately for cases with suspected HSR during the oral CAB/RPV lead-in phase and participants would not proceed to the injection phase. Any HSR reactions that occur would be managed supportively.
New site of intramuscular injection: *vastus lateralis*	Intramuscular CAB injections into the thigh (*vastus lateralis*) have not previously been administered in the CAB development program. Similar to the ventrogluteal region, the *vastus lateralis* is free of major nerves and blood vessels. Therefore, it is expected to be a safe site for injections. The *vastus lateralis* is part of a large muscle group and can tolerate high volume injections of up to 5ml [Rodger, 2000] in adults with lesser amounts being stipulated in younger participants or in those with less developed or atrophied muscle beds [Rodger, 2000]	• Training of the appropriate technique will be provided to staff at the study centre and will be described in the study manual • During the injection phase further enrolment and dosing of participants may be stopped if a participant develops a ≥Grade 3 related AE (including thigh injection site complications).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Venipuncture	Participants will be required to have blood samples taken, which entails, 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 applied and subsequently.	• ECGs will be conducted by appropriately trained personnel and effort made to minimize contact time for application of the pads.
Vasovagal reaction	Receiving injections can cause some participants to feel lightheaded or feel like they might pass out, or 'faint'. This reaction, called a 'vasovagal reaction', can occur with many medical procedures and resolves quickly.	• The participants are monitored and stay in the clinic for 2 hours after the injection for additional sampling and further observation.

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. Refer to 'Summary of data and guidance for the investigator'.

Seizure

Several cases of seizure have occurred during the CAB program. These cases have had alternative explanations for their occurrence. Overall, there is not convincing evidence that CAB 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 CAB. Participants with an unstable or poorly controlled seizure disorder will be excluded from study participation. Report any cases of seizure or seizure like events within 24 hours of the event.

2.3.2. Benefit Assessment

Participants participating in this study will not receive any clinical benefit but will be compensated for their time and participation.

Benefit considerations may include satisfaction from knowledge that participants have contributed to the process of developing new therapies for HIV.

2.3.3. Overall Benefit: Risk Conclusion

Review of the cumulative safety data on CAB and RPV have not identified any safety signals which are considered to pose an unacceptable risk to healthy participants.

Considering the multiple and overlapping measures that will be taken to minimize risk to participants participating in this study, the potential risks identified in association with CAB and RPV are justified by the anticipated benefits that may be afforded to participants including the satisfaction of contributing to the ongoing continued clinical development of CAB and RPV for both the treatment and prevention of HIV infection.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To describe the PK profiles of CAB and RPV following a single intramuscular injection each of CAB LA + RPV LA administered to the lateral thigh muscle in adult healthy participants	• Maximum observed concentration (Cmax) and time of maximum observed concentration (tmax) in plasma • Area under the concentration – time curve from time zero to last quantifiable time point (AUC(0-t)) through the follow-up phase • Area under the concentration – time curve from time zero to infinity (AUC0-∞) • Apparent terminal phase half-life (t½) and absorption rate constant (KALA))
Safety	
• To assess safety and tolerability of CAB and RPV following repeated oral dose and single intramuscular injection in the lateral thigh of adult healthy participants	• Safety and tolerability parameters including adverse events, clinical laboratory tests, ECG, and vital sign assessments

Objectives	Endpoints
Exploratory	
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a phase 1, open label study in healthy participants to assess the PK of CAB and RPV in plasma following a single 600 mg (1 x 3 mL) and a 900 mg (1 x 3 mL) injection each; respectively, administered IM to separate *vastus lateralis* muscles on each leg.

The study will consist of

- 30-day screening period
- 28-day oral lead-in (OLI) phase at a CAB dose of 30 mg and RPV dose of 25 mg once a day with a meal
- 10 – 14 days washout period
- CAB and RPV injection, administered IM: 600 mg (1 x 3 mL) CAB on left and a 900 mg (1 x 3 mL) RPV injection on right *vastus lateralis* muscle
- Sparse PK sampling for up to 29 days in OLI and serial PK sampling for up to 4 weeks after the injection, per SoA. Participants will return for safety assessments and additional PK sampling at Week 8, 12, 24, 36, and 52 post last injection during the follow-up phase.

Approximately 15 adult healthy participants will be dosed with injectable study interventions. If participants prematurely discontinue the study, for any other reason, other than an AE, additional replacement participants may be enrolled at the discretion of the Sponsor in consultation with the investigator.
Approximately 30% of female participants will be enrolled.

4.1.1. Screening

All participants will undergo a screening visit within 30 days of the first dose of the oral lead-in phase. Participants may be rescreened once. Participants who are enrolled into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may continue to the oral lead-in phase as soon as all eligibility requirements have been met.

4.1.2. Oral Lead-in Phase

Participants that are eligible to participate will be admitted to the clinic on Day 1 of the OLI phase and receive their first oral dose of CAB 30 mg and RPV 25 mg with a standard breakfast after the completion of all pre-dose assessments. Participants will undergo sparse PK sampling of blood as described in Schedule of Activities (SoA). After a pre-dose 24-hour PK sample collection and laboratory assessments, participants will take their Day 2 study interventions with a meal at the clinic. Participants will be dispensed a sufficient supply of oral CAB + RPV tablets to complete 26 days of once daily dosing at home (with exception of the visit days at the clinic) and be counseled to take their dose with a meal at about the same time each day, before getting discharged on Day 2.

On Day 14 of the OLI phase, the participants will return to the clinic. A pre-dose PK sample will be collected. In addition, this visit will include assessment of safety, tolerability, and participant adherence to study drug. Participants should bring their supply of oral CAB + RPV to the Day 14 visit to have drug accountability performed. Participants will receive Day 14 dose at the clinic.

Participants will return to the clinic on Day 29, within 24 hours of last dose on Day 28 for PK, drug accountability, and all assessments performed as described in the SoA Section 1.3. The participants will begin a wash-out period of 10-14 days, during which no CAB and RPV will be administered.

4.1.3. CAB and RPV Injection and PK Sampling

After the washout period of 10-14 days, participants will return to the clinic and receive an intramuscular injection of CAB LA (3 mL; 600 mg) on one lateral thigh and RPV LA (3 mL; 900 mg) into opposite lateral thigh on Injection Phase Day 1. Participants will remain in the research unit for at least 4 hours after the injection for PK sampling and safety assessments. Participants will return to clinic for PK sampling and safety assessments for 4 weeks as outlined in SoA.

4.1.4. Follow-up/Withdrawal Visit

Because of the long acting PK profile of CAB LA + RPV LA, every effort should be made to bring participants back in through the 52 weeks post injections. Participants, who received CAB LA + RPV LA IM injection, will return to clinic for safety and PK assessments at Weeks 8, 12, 24, 36, and 52 post IM injections.

If a participant is withdrawn:

- prior to receiving the IM injection, then a follow-up/withdrawal visit should be scheduled 10-14 days after the last oral dose of CAB + RPV.
- after receiving IM dose of CAB LA and/or RPV LA injections, every effort should be made to bring the participants back in for the 52 weeks of safety and PK assessments following the injection(s), because of the long acting PK profile of CAB and RPV.

4.2. Justification for Dose

4.2.1. Oral Dose:

The risk of developing a hypersensitivity reaction (HSR), post administration of CAB LA and RPV LA is minimized by the use of a 4-week OLI of oral CAB and RPV. In the event of a suspected HSR, participants will not receive CAB LA and RPV LA injections. The management of participants with HSRs following receipt of drugs with a long half-life may be challenging. HSRs have been reported as uncommon occurrences with integrase CAB and RPV, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. The time of onset of HSR reactions supports the proposed duration of the OLI with the majority of HSRs occurring within the first 28 days of exposure to the drugs.

During the OLI phase of this study, oral formulations of CAB + RPV will be co-administered to assess safety and tolerability in each participant prior to IM dosing with CAB LA and RPV LA. The combination of oral RPV 25 mg QD and CAB 10, 30, and 60 mg QD has been used as OLI in HIV-1 infected participants in both Phase IIb studies, the pivotal Phase 3 studies (FLAIR and ATLAS), and Phase 3b study ATLAS-2M.

In these studies, all three oral CAB doses demonstrated similar efficacy at the Week 48 primary endpoint. However, 30 mg dose was selected as OLI for all CAB LA studies, as it delivered higher steady-state exposures than predicted for the monthly or every 2-month regimen. CAB 30 mg is also the OLI treatment intended for marketing. Therefore, CAB 30 mg along with marketed dose of RPV 25 mg (EDURANT) will be used as the OLI dosing in this study and will achieve exposures sufficiently high to assess safety and tolerability during a short OLI prior to a single IM injection of CAB LA + RPV LA formulations.

The PK collected during the OLI phase will be utilized along with the data from LA injection phase to precisely estimate PK parameters using a robust population PK (PoPPK) model. A window of 10 to 14 days (covering ~7-10 half-lives) will be used for wash-out period prior to LA injection accounting for variability in half-life in participants. This wash-out period would prevent plasma concentrations after oral administration from being mixed with plasma concentrations on Day 1 after LA IM injection.

4.2.2. Long Acting Injectable Dose:

This study will evaluate the intramuscular administration of CAB LA (3 mL; 600 mg) and RPV LA (3 mL; 900 mg) into the lateral thigh muscle of left leg and right leg respectively.

The CAB LA + RPV LA Q4W regimen demonstrated noninferiority to oral standard of care (SOC) in pivotal Phase 3 studies. In those studies, gluteal injections were initiated with CAB LA 600 mg + RPV LA 900 mg (3mL each) followed by monthly injections of CAB LA 400 mg + RPV LA 600 mg (2mL each). An every 2-month dosing regimen of CAB LA 600 mg + RPV LA 900 mL is under investigation (3 mL of each drug for all injections). It is anticipated that absorption from the lateral thigh will be similar to gluteal and thus the current study will evaluate the intramuscular administration of CAB LA (3 mL; 600 mg) and RPV LA (3 mL; 900 mg) into the lateral thigh muscle of left leg and right leg respectively. Therefore, the terminal slope following the injection (lambda z) is expected to be similar in this study to population PK predictions of absorption rate constant (KALA) for CAB [overall population: 0.00064 hr^{-1} (0.0002, 0.0018)] and RPV [0.000145 h-1 (0.00014 – 0.00016)]. In addition, CAB and RPV concentrations for the current study are expected to fall within the range of concentrations observed following the first injections in the pooled FLAIR and ATLAS studies.

The following table lists the median, 5th, and 95th percentiles of evaluable trough concentrations of CAB and RPV following initial gluteal 3 mL injections from ATLAS and FLAIR studies. Furthermore, exposure parameters are anticipated to fall within the range of the model predictions following a single 3 mL gluteal IM injection as shown in Table 2.

Table 1 Observed Trough Concentrations Following First IM Injection in FLAIR and ATLAS Studies, Pooled Data

VISIT	ANALYTE	5th	50th	95th
WEEK 4	CAB	0.4521	1.57	3.5
WEEK 4	RPV	17.4	39.45	88.275

Table 2 Model Predicted Exposure Parameters of CAB and RPV Following A Single IM Injection in *Gluteus Medius*

Parameter	Units	CAB	RPV
		Median (90% PI)	Median (90% PI)
KALA	/h	0.00064 (0.0002, 0.0018)	0.000146 (0.000145, 0.000164)
Half-Life	Weeks	6.5 (2.3, 20.9)	28.1 (25.1 - 28.4)
Tmax	days	8 (5, 15)	4.0 (3.0 - 31.0)
Cmax	µg/mL	2.13 (0.69, 5.80)	56.0 (21.2 - 151)
C_{Wk4}	µg/mL	1.56 (0.63, 2.96)	34.6 (17.5 - 69.3)
C_{Wk8}	µg/mL	0.91 (0.43, 1.57)	20.3 (10.4 - 38.3)
C_{Wk12}	µg/mL	0.58 (0.18, 1.03)	13.5 (6.75 - 25.6)

Parameter	Units	CAB	RPV
		Median (90% PI)	**Median (90% PI)**
C_{Wk24}	µg/mL	0.18 (0.025, 0.45)	6.98 (3.33 - 13.6)
C_{Wk36}	µg/mL	0.05 (0.025, 0.26)	4.88 (2.26 - 9.68)
C_{Wk48}	µg/mL	0.025 (0.025, 0.16)	3.58 (1.66 - 7.15)
C_{Wk52}	µg/mL	0.025 (0.025, 0.14)	3.24 (1.50 - 6.49)
$AUC_{0\text{-}Wk4}$	µg*h/mL	1216 (422, 2857)	28354 (10674 - 67476)
$AUC_{0\text{-}Wk8}$	µg*h/mL	2080 (811, 4132)	47419 (21949 - 99140)
$AUC_{0\text{-}Wk12}$	µg*h/mL	2601 (1133, 4763)	58909 (29731 - 116809)
$AUC_{0\text{-}Wk24}$	µg*h/mL	3271 (1788, 5461)	78560 (43502 - 144786)
$AUC_{0\text{-}Wk36}$	µg*h/mL	3519 (2082, 5738)	91349 (51528 - 164003)
$AUC_{0\text{-}Wk48}$	µg*h/mL	3634 (2215, 5852)	100079 (56879 - 178154)
$AUC_{0\text{-}Wk52}$	µg*h/mL	3655 (2240, 5868)	102380 (58332 - 182124)

4.3. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the follow up visit Week 52.

The end of the study is defined as the date of the last visit of the last participant in 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.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range may be included only if the investigator in consultation with the Medical Monitor agree and document that the finding is unlikely to introduce additional risk and will not interfere with the study procedures. A single repeat of a procedure or laboratory parameter is allowed to determine eligibility.
4. Participants who are negative on two consecutive tests for SARS-CoV-2, performed at Screening and on Day -1 of admission to the Phase I unit, using an approved molecular test (PCR or antigen test).

Weight

5. Body weight ≥ 40 kg and body mass index (BMI) within the range 18 to 35 kg/m^2 (inclusive).

Sex

6. Male or female. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 52 weeks after the last dose of study intervention:

- Refrain from donating sperm

  Plus either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
  - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

b. Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    - Is not a woman of childbearing potential (WOCBP)

      OR

b. Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the intervention period and for at least 52 weeks after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive (Appendix 2) pregnancy test (urine or serum as required by local regulations) within 30 days of the first dose of study intervention.
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Signs and symptoms which in the opinion of the investigator are suggestive of COVID-19 (i.e. fever, cough etc) within 14 days of inpatient admission
2. Contact with known COVID-19 positive person/s in the 14 days prior to inpatient admission
3. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, neurological or psychiatric disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data

4. Abnormal blood pressure as determined by the investigator.
5. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
6. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
7. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
8. History of ongoing or clinically relevant seizure disorder within the previous 2 years, including participants who have required treatment for seizures within this time period. A prior history of seizure, with a seizure free period of at least 2 years, off anti-epileptics, may be considered for enrolment if the investigator believes the risk of seizure recurrence is low. All cases of prior seizure history should be discussed with the medical monitor prior to enrolment.
9. QTc >450 msec for male participants and >470 msec for female participants

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.
10. A participant, who has an underlying skin disease or disorder (i.e. infection, inflammation, dermatitis, eczema, drug rash, drug allergy, psoriasis, food allergy, urticaria).
11. A participant, who is considered to have insufficient musculature to allow safe administration of CAB or RPV in the opinion of the investigator will be excluded.

Prior/Concomitant Therapy

12. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication to the completion of the follow-up visit unless in the opinion of the Investigator and ViiV Medical Monitor the medication will not interfere with the study procedures or compromise participant safety. The use of any concurrent prohibited medications as outlined in Section 6.4.2.

Prior/Concurrent Clinical Study Experience

13. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days.
14. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

15. Participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

Diagnostic assessments

16. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention.
17. Positive Hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention.

NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

18. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention.

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

19. Presence of the Hepatitis B core antibody (HBcAb) should also lead to exclusion from the study even if HBsAg is negative.

Other Exclusions

20. Positive pre-study drug/alcohol screen
21. Positive human immunodeficiency virus (HIV) antibody test
22. Regular use of known drugs of abuse
23. Regular alcohol consumption within 6 months prior to the study defined as:
    - An average weekly intake of >14 units for males or >7 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
24. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening.
25. Participant, who has a tattoo or other dermatological condition overlying the thigh region which may interfere with interpretation of injection site reactions.
26. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

An overnight fast is preferred prior to screening laboratory assessments; however, a minimum of a 6 hour fast is acceptable. Otherwise, food and drink can be given ad libitum

throughout the course of the trial. At visits where participants will be in the clinic for multiple hours, meals will be provided by the study site (in the form of a boxed lunch or card for use at the site cafeteria).

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices during the oral lead in phase through Day 29 PK collection.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will abstain from alcohol for 48 hours prior to initiating oral dosing and prior to the injections. Participants will abstain from alcohol for 48 hours prior to the collection of the pharmacokinetic sampling and clinical laboratory tests.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests, and also the first 4 hours after injection. During this time, participants may participate in light recreational activities (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

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

Dosing and Administration

CAB + RPV Oral Lead-In Phase	
Day 1 to Day 28	Take one tablet of CAB 30 mg + RPV 25 mg once daily with a meal
CAB LA + RPV LA Injection Phase	
Injection Day 1	• 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

6.1. Study Interventions Administered

6.1.1. Formulations of CAB and 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/ViiV 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 Extended Release Suspension for Injection (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 stopper and aluminum seal. Each vial is for single-dose use containing a withdrawable volume of 2.0 mL (400 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 Extended Release Suspension for Injection (RPV LA))

RPV LA (TMC278, GSK1329758, 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 stopper and aluminum seal. Each vial contains a nominal fill of 2.0 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.

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

6.2. 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 will 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.

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).

Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual (SRM).

- 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/ViiV study contact.
- Precaution will be taken to avoid direct contact with the study intervention. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK/ViiV study contact.

6.2.1. 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(s) 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 or provided vial adapter to withdraw the required volume of suspension for IM injection.

All injections must be given intramuscularly in the thigh muscle, each injection on one thigh. The time and location of injection will be captured in the case report form (CRF).

Additional injections instructions can be found in the SRM.

6.3. Study Intervention Compliance

- 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 source documents. 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. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.
- When participants self-administer study intervention(s) at home, compliance with CAB + RPV dosing will be assessed through querying the participant during the site visits and documented in the source documents and CRF. IP accountability will be evaluated using pill counts of unused IP (CAB and RPV tablets).
- A record of the number of CAB + RPV tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.4. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) 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.

6.4.1. Permitted Medications and Non-Drug Therapies

Participants must abstain from taking prescription drugs within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants must abstain from taking non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until the last PK sample collected on Week 8, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen at doses of ≤ 2 grams/day is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

Oral CAB and RPV 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 oral CAB and RPV

- H2 antagonists must be taken at least 12 hours before or at least 4 hours after oral RPV oral RPV should not be co-administered with proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

6.4.2. Prohibited Medications and Non-Drug Therapies

For participants receiving **either formulation** of CAB and 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

- Rifapentine
- St. John's wort (*Hypericum perforatum*)

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

- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole;
- systemic dexamethasone (more than a single dose).
- anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.5. Dose Modification

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

6.6. Intervention after the End of the Study

Participants will not receive any additional treatment from GSK/ViiV Healthcare after completion of the study because only healthy participants are eligible for study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants may voluntarily withdraw from the study at any time and for any reason. Site investigators and study staff may withdraw participants before their scheduled termination visit for safety, behavioral, or administrative reasons, or if the participants are unable or unwilling to comply with study procedures. The reasons for withdrawals will be recorded in the participants' study records. 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.

During the oral lead-in period, early withdrawal on medical grounds will occur if the participant develops a Grade 3 or higher AE that is judged by the investigator to be related directly to the study product (see Appendix 3 and Appendix 4) for definitions and grading of severity of adverse events), or a participant develops a grade 3 or higher clinical significant laboratory abnormality (see Division of AIDS [DAIDS] table Appendix 7 for grading) or any AE that is deemed clinically significant by the investigator and is judged by the investigator to be related directly to the study product.

For liver-related stopping criteria, please refer to Section 7.1.1.

If a participant receives the injections, they will be followed 52-weeks post the final injection per protocol for appropriate procedures, including blood plasma PK sampling, and safety evaluations, and will not be removed from the study for medical reasons, unless they refuse to continue participation.

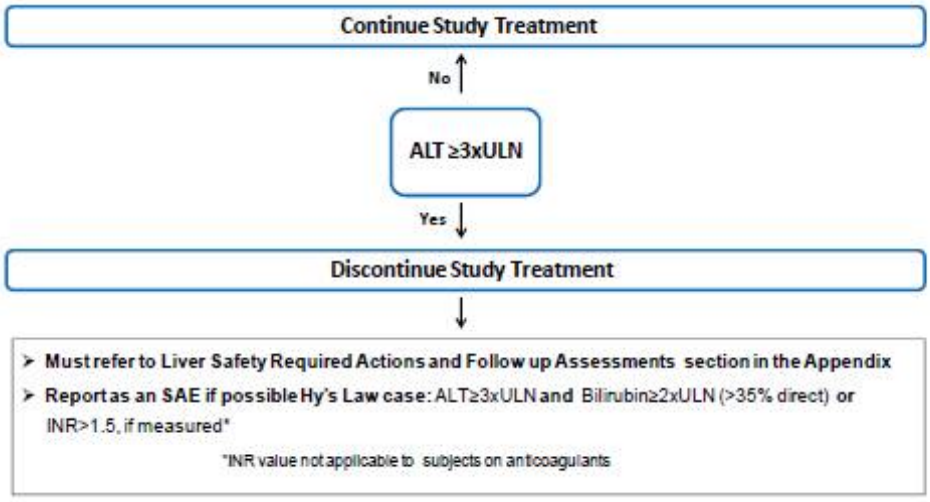
During the oral lead in phase additional pre-specified reasons for discontinuing a participant from the study (or, at minimum, discontinuing administration of study product and continuing safety evaluations) include:

- Pregnancy (please see Section 8.2.5)
- Protocol deviation
- Non-compliance
- Participant withdraws consent
- Participant lost to follow-up
- Investigator discretion
- Sponsor discontinues study

7.1.1. Liver Chemistry Stopping Criteria

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined or if the investigator believes that it is in the best interest of the participant.

Refer to Appendix 6 for required Liver Safety Actions and Follow up Assessments.

7.1.2. QTc Stopping Criteria

A participant that meets the bulleted criterion below will be withdrawn from the study.

- QTc > 500 msec
- QTc increase from baseline > 60 msec

- 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.

- The QTc should be based on the average of triplicate QTc values ECG readings obtained over a brief (e.g., 5-10 minute) recording period.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and 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.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

  If these assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

  - 12-lead ECG
  - vital signs
  - blood draws.

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time

- Protocol waivers or exemptions are not allowed
- Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
  - The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
  - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.1.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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

8.1.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.1.3. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. 12-lead ECGs will be performed with the subject in a supine position having rested in this position for at least 5 minutes beforehand.

8.1.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- 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 or within 7 days after the last dose of study intervention 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, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
    - **Screening for SARS-CoV-2**: Study participants will be monitored at Screening and daily while inpatients for COVID-19 symptoms. Investigator(s) should utilise the World Health Organisation (WHO)_Case Definitions to classify COVID-19 cases [World Health Organisation, 2020]. While outpatients, participants should report to the unit any symptoms suggestive of COVID-19. All participants who experience symptoms suggestive of COVID-19 should be

isolated in the unit or at home and tested for SARS-CoV-2 using an approved molecular test (PCR or antigen test). If a participant tests positive or becomes symptomatic with suspected/confirmed COVID-19 while on-unit, then the remaining participants in that cohort on the unit should be discharged). The investigator should consider any participant testing positive for SARS-CoV-2 being discontinued from study drug if COVID-19 symptoms are moderate to severe. Appropriate contact tracing for all participants testing positive will be performed within the unit. This should be done in accordance with local legislation and guidelines. Appropriate follow up should be implemented for participants who discontinue the study due to COVID-19.

8.1.5. Suicidal Ideation and Behavior Risk Monitoring

- Participants will be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

8.2. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

8.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention until the follow-up Week 52 visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK/ViiV product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up Week 52 visit at the time points specified in the SoA (Section 1.3).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. 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 to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.2.2. 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 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.2.3. 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, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 52-week post injections.
- If a pregnancy is reported, the investigator should inform GSK/ViiV within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3. Treatment of Overdose

For the oral lead in phase of this study, any dose of CAB > 30 mg and/or RPV > 25mg within a 24-hour time period will be considered an overdose.

For the injection phase of the study, any dose of CAB LA > 600 mg and/or RPV LA > 900 mg will be considered an overdose.

GSK/ViiV does not recommend specific treatment other than supportive care for an overdose.
The investigator will use clinical judgement to treat any overdose.
In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until CAB and/or RPV can no longer be detected systemically.
3. 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.

8.4. Pharmacokinetics

Blood samples of CAB (~ 2 mL each) and RPV (~ 2mL each) will be collected for measurement of plasma concentrations of CAB and RPV, respectively, as specified in the SoA.

- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling 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.

- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of CAB and RPV. Genetic analyses will not be performed on these plasma samples.

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

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.

Permitted sampling window for the OLI Phase:

Plasma PK Assessment	**Permitted Sampling Window**
Day 1 (1 h)	±15min
Day 1 (2 h)	±15min
Day 1 (3 h)	±30 min
Day 1 (4 h)	±15min
Day 1 (6 h)	±30 min
Day 1 (8 h)	±1h
Day 1 (12 h)	±1h
Day 2 (24 h)	±2h
Day 14	±1 day
Day 29	22-26h from Day 28 dose

Permitted sampling window for injection phase is provided in SoA.

8.5. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of genetic research samples can be found in the SRM.

8.6. Patient Reported Outcomes

Patient Reported Outcomes assessments will be conducted according to the SoA.

CCI

Additional information will be provided in SRM.

9. PHARMACOKINETIC METHOD OF ANALYSES

The department of Clinical Pharmacology Modelling & Simulation (CPMS) will be responsible for the PK data analysis of the CAB and RPV data.

PK analysis of the plasma CAB and RPV concentration-time data will be conducted using non-compartmental methods with WinNonlin (Version 6.3 or higher). Actual sampling and dosing times as recorded in eCRF will be used for analysis. From the plasma concentration-

time data, the following pharmacokinetic parameters will be determined, as data permit: AUC(0-∞), AUC(0-t), Cmax, tmax, half-life ($t_{½}$), and absorption rate constant (KALA).

Plasma CAB and RPV concentration data will be presented in graphical and/or tabular form and will be descriptively summarized.

Details of PK analyses will be provided in the report and analysis plan (RAP) separately.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

The primary objective of this study is to evaluate the pharmacokinetics of CAB and RPV following a single intramuscular administration of each in the lateral thigh of healthy adult participants. No formal statistical hypotheses are to be tested. Where appropriate, an estimation approach will be taken and point estimates and confidence intervals will be constructed.

10.2. Sample Size Determination

There was no formal calculation of power or sample size for this study. Approximately 15 participants will receive CAB LA + RPV LA IM injections and provide informative safety and pharmacokinetic data based on feasibility considerations.

10.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Safety	All participants who take at least 1 dose of study drug.
Pharmacokinetic Concentration	All participants who undergo plasma PK sampling and have evaluable PK assay results. This population will be used for the concentration listing.
Pharmacokinetic Parameter	All participants who undergo plasma PK sampling and have evaluable PK parameters estimated. This population will be used for PK parameter listing, plotting of the concentration-time data and PK parameter summary.

10.4. Statistical Analyses

The statistical analysis plan will be finalized prior to Database Release (DBR) and it will include a more technical and detailed description of the statistical analyses described in

this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

10.4.1. General Considerations

Final analysis will be performed after the completion of the study and final datasets authorization. Data will be listed and summarized according to GSK reporting standards, where applicable.

Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), median, minimum, and maximum for continuous variables, whereas n and percent will be used as summary statistics for categorical variables. For PK data, coefficient of variation (%CV), geometric mean with associated 95% confidence interval (CI), and the between- participant CV (%CVb) for the log-transformed PK parameters will also be provided as appropriate.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.4 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings. Complete details will be documented in the RAP.

10.4.2. Primary Endpoint(s)

Descriptive statistics and/or graphics will be created to describe the primary endpoints of interest. Concentrations will be determined directly from concentration-time data from each matrix. Data will be presented in tabular and or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical testing will be conducted.

Pharmacokinetic analyses will be the responsibility of Clinical Pharmacokinetics Modeling & Simulation Department within GSK. Plasma CAB and RPV concentration-time data will be analyzed by non-compartmental methods with WinNonlin Professional 5.2 or higher, Phoenix (Pharsight Corporation) or comparable software. Calculations will be based on the actual sampling times recorded during the study.

The following pharmacokinetic parameters will be determined, as data permits, for the PK profile of CAB LA + RPV LA:

- maximum observed concentration (Cmax)
- time of maximum observed concentration (tmax)
- area under the concentration-time curve from time zero to last quantifiable time point (AUC(0-t))
- area under the concentration-time curve from time zero to infinity (AUC(0-∞))
- apparent terminal phase half-life (t½)
- absorption rate constant (KALA)

10.4.3. Secondary and Safety Endpoint(s)

All secondary and safety analyses will be performed on the Safety Population. AEs will be summarized using MedDRA preferred terms. All AEs, drug-related AEs, SAEs, liver-related AEs and AEs leading to permanent discontinuation of study drug or withdrawal will be summarized or listed. AEs and drug-related AEs will also be summarized by maximum toxicity grade (based on DAIDS categories). Laboratory data, vital signs and ECG data (absolute values and change from Baseline) will be summarized by visit. Liver chemistry abnormalities will be summarized or listed. Details will be documented in the RAP.

10.5. Interim Analyses

There is no planned formal interim analysis. All preliminary safety, tolerability and available pharmacokinetic data may be reviewed internally at any time point. Depending on feasibility, evaluation of PK data may be performed at time points such as Week 4 and Week 12 post injection for preparatory PK modelling.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus of 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.

11.1.2. 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.

11.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant 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.

GSK/ViiV (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study intervention and the injection site; publish the results of these research efforts; work with government agencies or insurers to have the study intervention approved for medical use or approved for payment coverage.

11.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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.

11.1.5. 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/ViiV site or other mutually-agreeable location.
- GSK/ViiV 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/ViiV 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 patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

11.1.6. 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 15 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.

11.1.7. 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.
- Definition of what constitutes source data can be found in Monitoring Plan.

11.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

GSK/ViiV 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//ViiV. 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 the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up, if required.

11.1.9. 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.

11.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted per SoA.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments[1]	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean Corpuscular Volume Mean Corpuscular Hemoglobin %Reticulocytes	White Blood Cell count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[2]	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose fasting	Calcium	Alkaline phosphatase	
Coagulation tests	Prothrombin Time	Partial Thromboplastin Time	International Normalized Ratio	

Laboratory Assessments[1]	**Parameters**
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• HIV: HIV 1-2 antibody/antigen (Ab/Ag) testing • Hepatitis B screen: Hepatits B surface antigen (HBsAg) • Hepatitis B surface antibody(HBsAb), and Hepatitis core antibody (HBcAb) • Hepatitis C (Hep C antibody) • Alcohol screen and drugs of abuse screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine (or serum) human Chorionic Gonadotropin Pregnancy test (as needed for women of child bearing potential)[4] The results of each test must be entered into the CRF.

NOTES:
1. An overnight fast is preferred prior to screening laboratory assessments; however, a minimum of a 6 hour fast is acceptable.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

11.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.3.1. 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). Note: Clinically significant laboratory abnormalities captured as AEs should be graded as per the clinical AE grade criteria, rather than by laboratory grade to be graded by the central laboratory or central statistical analysis group using DAIDS laboratory grading criteria as per • 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. • 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.

11.3.2. 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 or significant 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 (e.g. 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 and impaired liver function defined as:

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

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

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

11.3.3. 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 (e.g. 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 per Appendix 7:

- 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.

11.3.4. Reporting of SAE to GSK

SAE Reporting to GSK/ViiV 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/ViiV 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.

11.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

11.4.1. Definitions:

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.

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.

11.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• 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** *Failure rate of <1% per year when used consistently and correctly.*

• 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. 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. Male condom and female condom should not be used together (due to risk of failure with friction)

11.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while participating in this study. This applies only to male participants who receive CAB + RPV.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial 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 (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) 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 3. 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 in OLI phase. will discontinue study intervention if participant gets pregnant and will not receive IM injections.
If participant gets pregnant after receiving CAB LA and RPV LA, the participant should be followed up through 52 weeks post injections.

11.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to CAB and/or RPV. They may also be used to develop tests/assays including diagnostic tests related to CAB and/or RPV and other medicines used to treat or prevent HIV infection. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate)
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to CAB and/or RPV or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on CAB and/or RPV (or study interventions of this class) or and other medicines used to treat or prevent HIV infection continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

11.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or <u>international normalized ratio (INR)</u> >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained CAB + RPV of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake CRF</td></tr>
</table>

Liver Chemistry Stopping Criteria	
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) [James, 2009]. **NOTE: not required in China**. • 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.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. 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 SRM.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA,et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

11.7. Appendix 7: 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 utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

The table can be found at:

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 - July 2017)

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

11.8. Appendix 8: Permissible Procedures during the COVID-19 Pandemic

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 participant's ability to attend clinic visits. Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to allow flexibility to allow conduct of the study.

Permissible changes to procedures during the COVID-19 pandemic if deemed necessary by the investigator are outlined below. The investigator should discuss with the medical monitor the rationale if any of these changes are required for a participant. For further details refer to the Study Reference Manual (SRM).

- Participants previously deemed eligible during the screening period unable to attend within the allowable screening window due to COVID-19 may be rescreened.
- Oral CAB dosing Days 1 to 28. All doses except Day 1 and Day 14 may be administered at home if participants are unable to attend due to COVID-19.
- AE assessments during the oral lead in may be conducted by telephone at home if participants are unable to attend due to COVID-19.
- Duration of admission to the clinic may be extended if deemed necessary by the investigator due to the COVID-19 pandemic.
- The 10 to 14-day washout period after the oral lead in may be extended if deemed necessary by the investigator due to the COVID-19 pandemic.
- If a participant has suspected COVID-19, or tests positive for COVID-19, or has potential COVID19 exposure while enrolled in the study, the Investigator must assess the impact of this disease/situation on the benefit/risk for the participant(s) to continue in the study, as well as if the participant has met protocol withdrawal criteria. Any adverse events related to the COVID-19 infection should continue to be evaluated as to whether they meet SAE criteria as defined in Section 11.3.2., and if so, reported in line with the SAE reporting requirements (Section 11.3.4). Investigator(s) should utilise WHO Case Definitions to classify COVID-19 cases [World Health Organisation, 2020]. The Sponsor recognises that COVID-19 case definitions may evolve during the study period, the most recent edition should be consulted for each case. For all AEs or SAEs related to COVID-19, details should also be entered into the specific COVID-19 eCRF. The study site should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation in the setting of clinically defined mild COVID-19 infection.

11.9. Appendix 9: Abbreviations and Trademarks

AC	Active control
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-τ)	Area under the concentration-time curve over one dosing interval
AUC(0-24)	Area under the concentration-time curve over 24 hours
hCG	Human Chorionic Gonadotropin
BMI	Body mass index
BUN	Blood urea nitrogen
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
Cτ	Last observed quantifiable concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacokinetics Modelling & Simulation
CRF	Case Report Form
CV	Coefficient of variance
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FDA	Food and Drug Administration
FPFV	First participant First Visit
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilence
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
HSR	Hypersensitivity Reactions
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug

IP	Investigational Product
IRB	Institutional Review Board
ISRs	Injection Site Reactions
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
λz	Terminal phase rate constant
L	Liter
LA	Long Acting
LFTs	Liver function tests
µg	Microgram
µL	Microliter
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
NNRTI	Non-nucleoside reverse transcriptase inhibitor
OLI	Oral Lead In
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
PoPPK	Population PK
QC	Quality control
QD	Once daily
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
RPV	Rilpivirine
SAE	Serious adverse event(s)
SARS-CoV2/ COVID-19	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SRM	Study Reference Manual
STR	Study Team safety & PK Review

SUSAR	Suspected, Unexpected, Serious Adverse drug Reaction
t½	Terminal phase half-life
τ	Dosing interval
tmax	Time of occurrence of Cmax
UGT	UDP glucuronosyltransferase
ULN	Upper limit of normal
VSLC	ViiV Safety and Labelling Committee
US	United States
WBC	White blood cells
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of ViiV Healthcare
None

Trademarks not owned by the ViiV Healthcare
EDURANT

11.10. Appendix 10: Protocol Amendment History

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

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 1	*13-AUG-2020*	*2018N357118_01*
Original Protocol	*02-MAR-2020*	*2018N357118_00*

12. REFERENCES

ATLAS-2M: press release https://viivhealthcare.com/en-gb/media/press-releases/2018/viiv-healthcare-reports-positive-48-week-results-for-first-pivotal-phase-iii-study-for-novel-long-acting-injectable-hiv-treatment-regimen/

Chevat C, Viala-Dante M, et al. Development and psychometric validation of a self-administered questionnaire assessing the acceptance of influenza vaccination: the Vaccinees' Perception of Injection (VAPI©) questionnaire. Health Qual Life Outcomes. 2009; 7: 21.

Edurant Prescribing Information, June 2019.

Ford S, Margolis D, Chen S, Gould E, Spreen W. Plasma and tissue GSK1265744 pharmacokinetics following long-acting parenteral administration in healthy male and female subjects. Published at: International Workshop on Clinical Pharmacology of HIV Therapy 2013 - 14th Annual; April 22-24, 2013; Amsterdam, The Netherlands.

GlaxoSmithKline Document Number RH2009/00003/09: GSK1265744 (Cabotegravir) Clinical Investigator's Brochure, Version 09, December 2019.

Margolis D, Sutton K, Vente J, LeBlanc R et al. Long-Term Efficacy, Safety and Durability of CAB and RPV as Two Drug Oral Maintenance Therapy – LATTE Week 312 Result –IDWeek 2019

Margolis DA, Gonzalez Garcia J, Stellbrink H-J, et al. Safety, efficacy and durability of long-acting CAB and RPV as two drug IM maintenance therapy for HIV-1 infection: LATTE-2 week 160 results. Presented at: HIV Drug Therapy Glasgow 2018

NATAP report: R Verloes, G vanÔt Klooster, L Baert, F van Velsen,M-P Bouche, K Spittaels, J Leempoels, P Williams, G Kraus, P Wigerinck: TMC278 long acting - a parenteral nanosuspension formulation that provides sustained clinically relevant plasma concentrations in HIV-negative volunteers XVII International AIDS Conference, Mexico City August 2008

Orkin C, Arasteh K, Hernandez-Mora MG, et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: FLAIR week 48 results. Published at: Conference on Retroviruses and Opportunistic Infections - 26th Annual; March 4-7, 2019; Seattle, WA.

Rilpivirine Clinical Investigator Brochure [RPV IB], Edition Version 12 (18-Jul-2019).

Rodger MA, King L. Drawing up and administering intramuscular injections: a review of the literature. J Adv Nurs. 2000;31(3):574-582.

Spreen W, Williams P, Ford SF, et al. Repeat dose co-administration of GSK1265744 and TMC278 long-acting parenteral nanosuspensions: pharmacokinetics, safety, and tolerability in healthy subjects. Published at: International AIDS Society 2013 - 7th Conference on HIV Pathogenesis, Treatment & Prevention; Jun 30-July 3, 2013: Kuala Lumur, Malaysia.

Swindells S, Andrade-Villanueva J-F, Richmond G, et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: ATLAS week 48 results. Published at: Conference on Retroviruses and Opportunistic Infections - 26th Annual; March 4-7, 2019; Seattle, WA.

World Health OrganisationMarch 2020: Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim guidance. Available at: https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov). Accessed 18 June 2020.