TITLE PAGE

Protocol Title: A Phase IIIb, Randomized, Multicenter, Active-controlled, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Long-acting Cabotegravir Plus Long-acting Rilpivirine administered every two months from a Bictegravir/emtricitabine/tenofovir alafenamide Single Tablet Regimen in HIV-1 Infected Adults who are Virologically Suppressed

Protocol Number: 213500/ 03

Compound Number or Name: GSK1265744/Cabotegravir

Study Phase: IIIB

Short Title: PH3b, CAB LA + RPV LA vs BIK, IM Every 2 Months, Non-inferiority, Efficacy and Safety Study in Participants with HIV-1 Who are Virologically Suppressed

SOLAR (**S**witch **O**nto **L**ong **A**cting **R**egimen)

Sponsor Name and Legal Registered Address:

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

Sponsor Name and Legal Registered Address (excluding US):

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

US IND Sponsor Legal Registered Address:

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

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

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

Regulatory Agency Identifying Number(s):

IND No. 109,678

EudraCT No. 2020-002623-11

Approval Date: 10-FEB-2022

SPONSOR SIGNATORY:

Protocol Title: A Phase IIIb, Randomized, Multicenter, Active-controlled, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Long-acting Cabotegravir Plus Long-acting Rilpivirine administered every two months from a Bictegravir/emtricitabine/tenofovir alafenamide Single Tablet Regimen in HIV-1 Infected Adults who are Virologically Suppressed

Protocol Number: 213500/ 03

Compound Number or Name: GSK1265744/Cabotegravir

Sherene Min
VP and Head, Clinical Development
ViiV Healthcare

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	*10-FEB-2022*
Amendment 2	*8-SEP-2021*
DEU Amendment 1	*12-JAN-2021*
GBR Amendment 1	*20-NOV-2020*
FR Amendment 1	*16-NOV-2020*
Amendment 1	*30-JUN-2020*
Original Protocol	*27-MAY-2020*

Amendment 03: 10-FEB-2022
This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 03:

The primary reason for protocol amendment 03 is to address and clarify comments raised during the course of the study

Section # and Name	Description of Change	Brief Rationale
Headers	Change to protocol reference number	Due to sponsor protocol writing procedures
Section 1.1. Synopsis and Section 3 Objectives	Removed endpoint “Change from Baseline in incident metabolic syndrome at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I) in Metabolic Syndrome Objective	Not required
Section 1.1. Synopsis and Section 3 Objectives	Removed reference to BIK in the endpoint addressing Preference objective	Not required
Section 1.3 Schedule of Assessments	Removal of height, weight, (BMI), waist and hip circumference assessments in “BIK to Direct to Injection” arm at Month 14	Assessments not required
Section 1.3 Schedule of	Footnote aa. Addition of text	BIK Participant who withdraw at or

Section # and Name	Description of Change	Brief Rationale
Assessments	at the end: "Participants who do not enter Extension Phase or do not wish to transition to the commercial supply will not receive 1-month supply at M12."	after M12 will no longer be eligible for study BIK
Section 4.1.3 Extension Phase	Additional text provided on participants who transition to commercial product that the transition plan to marketed product should be done in consultation with the Central Study Team and study Medical Monitor	To provide adequate patient management during transition
Section 4.1.3.2 Participants Entering from BIK arm	Added text to remind Investigators to refer to list of prohibited medications	To ensure there is not risk of drug-drug interaction
Section 4.5 End of Study Definitions	Clarification on phone versus in-clinic safety Follow-up visits	For clarification purposes
Section 5.5.2 Cosmetic Surgery	Paragraph expanded	For clarification purposes

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase IIIb, Randomized, Multicenter, Active-controlled, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Long-acting Cabotegravir Plus Long-acting Rilpivirine administered every two months from a Bictegravir/emtricitabine/tenofovir alafenamide Single Tablet Regimen in HIV-1 Infected Adults who are Virologically Suppressed

Short Title: PH3b, CAB LA + RPV LA vs BIK, IM Every 2 Months, Non-inferiority, Efficacy and Safety Study in Participants with HIV-1 Who are Virologically Suppressed

Rationale: Study 213500 (**SOLAR**: **S**witch **O**nto **L**ong **A**cting **R**egimen) is designed to demonstrate the non-inferior antiviral activity of CAB LA 600 mg + RPV LA 900 mg administered every 2 months (Q2M) compared to Biktarvy (BIK) administered orally once daily for 12 months. The study will provide important comparative antiviral activity, safety and tolerability data of these regimens through Month 12 of the Maintenance Phase of the study as well as provide important comparative data on the optional oral lead in and anthropometric measures.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
To demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every two months compared to a BIK single tablet regimen administered once daily over 12 months in suppressed HIV-1 infected antiretroviral therapy (ART)-experienced participants	Proportion of participants with plasma HIV-RNA greater than or equal to 50 copies/mL as per Food and Drug Administration (FDA) Snapshot algorithm at Month 12 (OLI and BIK)/Month 11 (D2I) (Intent-to-Treat Exposed [ITT-E] population)
Secondary	
To demonstrate the antiviral and immunologic response with the use of CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen administered once daily	Proportion of participants with plasma HIV-1 RNA <50 c/mL (c/mL) at Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I) using the FDA Snapshot algorithm (Intent-to-Treat Exposed [ITT-E] population) Proportion of participants with protocol-defined confirmed virologic failure (CVF) through Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).

Objectives	**Endpoints**
	Proportion of participants with HIV-RNA greater than or equal to 50 c/mL as per FDA Snapshot algorithm at Month 6, and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I) Absolute values and changes from Baseline in viral load and CD4+ cell count over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I)
To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, BIC, FTC, and TAF through Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in participants treated with CAB LA + RPV LA compared to BIK	Change from Baseline (Day 1) in renal and bone biomarkers at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I).
To evaluate Metabolic Syndrome for participants treated with CAB + RPV and BIK	Change from Baseline in proportions of participants with Metabolic syndrome at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I)
To evaluate insulin resistance in participants treated with CAB LA + RPV LA compared to BIK	Change from Baseline (Day 1) in homeostasis model of assessment-insulin resistance (HOMA-IR) at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I).
To assess preference for CAB LA + RPV LA administered every 2 months compared to a BIK single tablet regimen administered once daily	Preference for CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen will be assessed using a preference questionnaire at Month 12 (OLI)/Month 11 (D2I) (or Withdrawal).
To assess patient reported treatment satisfaction, and injection tolerability.	Change from baseline (Day 1) in total “treatment satisfaction” score, and individual item scores of the HIV Treatment Satisfaction Status Questionnaire (HIVTSQs) at Month 6 and

Objectives	Endpoints
	Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I), (or Withdrawal) Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire HIVTSQc total score and individual item scores at Month 12 (OLI and BIK)/Month 11 (D2I) (or Withdrawal). Change from Month 2 in Dimension scores ("Acceptance of ISRs", "Bother of ISRs", "Leg movement", "Sleep") and individual item scores (assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time) will be assessed using the Perception of injection questionnaire (PIN) at Months 2, 6, and 12 (OLI)/Months 1, 5, 11 (D2I) (or Withdrawal)
Safety	
To evaluate the safety and tolerability of CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen administered once daily	Incidence and severity of AEs and laboratory abnormalities over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I). Proportion of participants who discontinue treatment due to AEs over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I). Change from Baseline in laboratory parameters over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).

Overall Design: This study is a Phase IIIb, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of a two-drug regimen of CAB LA + RPV LA administered every 2 months compared with maintenance of BIK. Approximately 654 adult HIV-1 infected patients who are on the stable ARV regimen BIK will be randomized 2:1 to either be switched to

the CAB LA + RPV LA regimen or continue BIK through 12 months. The study will continue with an Extension Phase after Month 12 (OLI and BIK)/Month 11 (D2I).

Disclosure Statement: This is an Intervention Model (Parallel) Primary Purpose (Treatment) study with Number Arms (2) that is masking (No Masking).

Number of Participants: A total of 654 participants with a 2:1 randomization ratio to either CAB LA+RPV LA or BIK is such that the study has approximately 85% power to demonstrate non-inferiority in the proportion of participants with snapshot virologic failure at Month 12 using a 4% margin, assuming a true 2% failure rate for CAB LA + RPV LA and a 1% failure rate for the BIK arm using a 2.5% one-sided alpha level. The randomized portion of the study will continue for 12 months with an Extension Phase.

Intervention Groups and Duration:

IM Injections every 2 months (Oral Lead In):

Day 1 – CAB 30 mg + RPV 25 mg oral, administered once daily for 1 month

Month 1 – CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

Month 2 - CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

Month 4 and Q2M thereafter - CAB LA 600 mg + RPV LA 900 mg IM, every 2 months until Month 12, each given as 1 X 3 mL IM injection

IM Injections every 2 months (Direct to Injections):

Day 1- CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

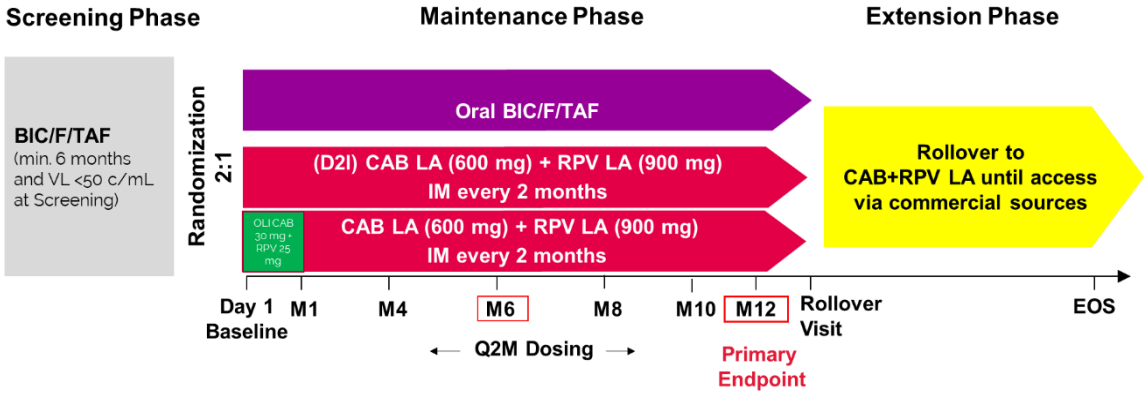
Month 1 and Q2M thereafter- CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

BIC/FTC/TAF (BIK)

Day 1 – BIC 50 mg + FTC 200 mg + TAF 25 mg oral, administered once daily until Month 12.

Data Monitoring or Other Committee: No

1.2. Schema


Screening Phase
Maintenance Phase
Extension Phase
BIC/F/TAF
(min. 6 months and VL <50 c/mL at Screening)
Randomization 2:1
Oral BIC/F/TAF
(D2I) CAB LA (600 mg) + RPV LA (900 mg) IM every 2 months
OLI CAB 30 mg + RPV 25 mg
CAB LA (600 mg) + RPV LA (900 mg) IM every 2 months
Rollover to CAB+RPV LA until access via commercial sources
Day 1 Baseline
M1
M4
M6
M8
M10
M12
Rollover Visit
EOS
Q2M Dosing
Primary Endpoint

1.3. Schedule of Activities (SoA)

Time and Events Table for CAB LA + RPV LA Oral Lead In (OLI) Participants:

Procedure	Screening Visit [a]	Maintenance Phase								Extension Phase	Withdrawal Assessments[y]	Long-Term Follow-up [z]
		Day 1[b]	Month 1[c]	2	4	6	8	10	12	Q2M after Month 12		
Written Informed Consent	X											
Eligibility Verification (Inclusion/ Exclusion Criteria)	X	X[d]										
Randomization		X										
Demography	X											
Medical History[e]	X											
Cardiovascular risk assessment[e]	X	X							X		X	
Medication History/ Prior ART history	X											
Syphilis serology + reflex Rapid Plasma Reagin (RPR)	X	X										
Symptom Directed Physical Exam and Medical Assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X
Weight, Height and BMI[g]		X		X	X	X			X		X	
Waist Circumference		X		X	X	X			X		X	
Hip Circumference		X		X	X	X			X		X	
Vital Signs (BP, HR, Temperature)[h]	X	X		X	X	X			X		X	
[redacted]												
12-lead ECG[i] (triplicate at Day 1 pre-dose)	X	X	X						X		X	
CDC HIV-1 stage[ff]	X	X										
HIV Associated Conditions		X	X	X	X	X	X	X	X	X	X	X
AEs, SAEs, Concomitant Medications	X[j]	X	X	X	X	X	X	X	X	X	X	X
ISR Assessment for IM injection			X	X	X	X	X	X	X	X	X	X

Procedure	Screening Visit [a]	Maintenance Phase								Extension Phase	Withdrawal Assessments[y]	Long-Term Follow-up [z]
		Day 1[b]	Month									
			1[c]	2	4	6	8	10	12	Q2M after Month 12		
Columbia Suicide Severity Rating Scale (eC-SSRS) [k]	X	X		X		X			X		X	
Clinical chemistry and Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[l]	S	U	U	U	U	U	U	U	U	U	S	U
HIV-1 RNA and sample for storage (S)[m]	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 RNA low copy sample		X							X			
CD4+ cell count	X	X	X	X	X	X	X	X	X	X	X	X
CD8+ cell count		X				X			X		X	
Urinalysis[n]		X	X			X			X		X	
Fasting Labs Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides[o]		X				X			X		X[p]	
Hepatitis B (HBsAg), Anti-HBc, and Anti-HBsAG, Hepatitis C (anti-HCV Ab)	X											
PT/PTT/INR	X	X										
Whole Blood (Virology)		X				X			X		X	
CCI												
PBMCs [q]		X				X			X		X	
Insulin, HbA1c and renal, and bone biomarker analytes (blood urine)[r]		X				X			X		X[x]	
CCI												
Genetics sample [t]		X										
PK sampling [u] (S)=Storage only			S	S	S	S	S	S	S		X	S
Oral CAB and Oral RPV Dispensation [v]		X										

Procedure	Screening Visit [a]	Maintenance Phase							Extension Phase	Withdrawal Assessments[y]	Long-Term Follow-up [z]
		Day 1[b]	Month								
			1[c]	2	4	6	8	10	12	Q2M after Month 12		
IP accountability (Pill Counts)			X									
IM treatment administration [w]			X	X	X	X	X	X	X	X		
HIV TSQs[cc]		X				X			X		X[dd]	
HIV TSQc[cc]									X		X[dd]	
CCI												
Preference[cc]									X		X[dd]	
PIN[cc]				X		X			X		X[dd]	
CCI												
History of Cosmetic procedures[gg]									X		X	

Time and Events Table for CAB LA + RPV LA Direct to Injection (D2I) Participants:

Procedure	Screening Visit [a]	Maintenance Phase						Extension Phase	Withdrawal Assessments[y]	Long-Term Follow-up [z]
		Day 1[b]	Month							
			1[c]	3	5	7	9	11	Q2M after Month 11		
Written Informed Consent	X										
Eligibility Verification (Inclusion/ Exclusion Criteria)	X	X[d]									
Randomization		X									

Procedure	Screening Visit [a]	Maintenance Phase							Extension Phase	Withdrawal Assessments[y]	Long-Term Follow-up [z]
		Day 1[b]	Month								
			1[c]	3	5	7	9	11	Q2M after Month 11		
Demography	X										
Medical History[e]	X										
Cardiovascular risk assessment[e]	X	X						X			
Medication History/ Prior ART history	X										
Syphilis serology + reflex Rapid Plasma Reagin (RPR)	X	X									
Symptom Directed Physical Exam and Medical Assessment[f]	X	X	X	X	X	X	X	X	X	X	X
Weight, Height and BMI[g]		X	X	X	X			X		X	
Waist Circumference		X	X	X	X			X		X	
Hip Circumference		X	X	X	X			X		X	
Vital Signs (BP, HR, Temperature)[h]	X	X	X	X	X			X		X	
CCI											
12-lead ECG[i] (triplicate at Day 1 pre-dose)	X	X						X		X	
CDC HIV-1 stage[ff]	X	X									
HIV Associated Conditions		X	X	X	X	X	X	X	X	X	X
AEs, SAEs, Concomitant Medications	X[j]	X	X	X	X	X	X	X	X	X	X
ISR Assessment for IM injection		X	X	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (eC-SSRS) [k]	X	X	X		X			X		X	
Clinical chemistry and Hematology	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[l]	S	U	U	U	U	U	U	U	U	S	U
HIV-1 RNA and sample for storage (S)[m]	X	X	X	X	X	X	X	X	X	X	X
HIV-1 RNA low copy sample		X						X			
CD4+ cell count	X	X	X	X	X	X	X	X	X	X	X
CD8+ cell count		X			X			X		X	

Procedure	Screening Visit [a]	Maintenance Phase							Extension Phase	Withdrawal Assessments[y]	Long-Term Follow-up [z]
		Day 1[b]	Month								
			1[c]	3	5	7	9	11	Q2M after Month 11		
Urinalysis[n]		X	X		X			X		X	
Fasting Labs: Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides[o]		X			X			X		X[p]	
Hepatitis B (HBsAg), Anti-HBc, and Anti-HBsAG, Hepatitis C (anti-HCV Ab)	X										
PT/PTT/INR	X	X									
Whole Blood (Virology)		X			X			X		X	
CCI											
PBMCs [q]		X			X			X		X	
Insulin, HbA1c and renal, and bone biomarker analytes (blood urine)[r]		X			X			X		X[x]	
CCI											
Genetics sample [t]		X									
PK sampling [u] (S)=Storage only			S	S	S	S	S	S		X	S
IM treatment administration		X	X	X	X	X	X	X	X		
HIV TSQs[cc]		X			X			X		X[dd]	
HIV TSQc[cc]								X		X[dd]	
CCI											
Preference[cc]								X		X[dd]	
PIN[cc]			X		X			X		X[dd]	
CCI											
History of Cosmetic procedures[gg]								X		X	

Time and Events Table for BIK Participants:

Procedure	Screening Visit [a]	Maintenance Phase							Withdrawal Assessments[y]
		Day 1[b]	Month						
			2	4	6	8	10	12[bb]	
Written Informed Consent	X								
Eligibility Verification (Inclusion/ Exclusion Criteria)	X	X[d]							
Randomization		X							
Demography	X								
Medical History[e]	X								
Cardiovascular risk assessment[e]	X	X						X	
Medication History/ Prior ART history	X								
Syphilis serology + reflex Rapid Plasma Reagin (RPR)	X	X							
Symptom Directed Physical Exam and Medical Assessment[f]	X	X	X	X	X	X	X	X	X
Weight, Height and BMI[g]		X	X	X	X			X	X
Waist Circumference		X	X	X	X			X	X
Hip Circumference		X	X	X	X			X	X
Vital Signs (BP, HR, Temperature)[h]	X	X	X	X	X			X	X
CCI									
12-lead ECG[i] (triplicate at Day 1 pre-dose)	X	X						X	X
CDC HIV-1 stage[ff]	X	X							
HIV Associated Conditions		X	X	X	X	X	X	X	X
AEs, SAEs, Concomitant Medications	X[j]	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (eC-SSRS)[k]	X	X	X		X			X	X
Clinical chemistry and Hematology	X	X	X	X	X	X	X	X	X
Pregnancy Testing[l]	S	U	U	U	U	U	U	U	S
HIV-1 RNA and sample for storage (S)[m]	X	X	X	X	X	X	X	X	X

Procedure	Screening Visit [a]	Maintenance Phase							Withdrawal Assessments[y]
		Day 1[b]	Month						
			2	4	6	8	10	12[bb]	
HIV-1 RNA low copy sample		X						X	
CD4+ cell count	X	X	X	X	X	X	X	X	X
CD8+ cell count		X			X			X	X
Urinalysis[n]		X			X			X	X
Fasting Labs Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides[o]		X			X			X	X[p]
Hepatitis B (HBsAg), Anti-HBc, and Anti-HBsAG, Hepatitis C (anti-HCV Ab)	X								
PT/PTT/INR	X	X							
Whole Blood (Virology)		X			X			X	X
CCI									
PBMCs [q]		X			X			X	X
Insulin, HbA1c and renal, and bone biomarker analytes (blood urine)[r]		X			X			X	X[x]
CCI									
Genetics sample [t]		X							
BIK Dispensation		X	X	X	X	X	X	X[aa]	
IP accountability (Pill Counts)			X	X	X	X	X	X	
HIV TSQs[cc]		X			X			X	X[dd]
HIV TSQc[cc]								X	X[dd]
CCI CCI									
History of Cosmetic procedures[gg]								X	X

Time and Events Table for BIK to Oral Lead In – Extension Phase:

Procedure	Extension Phase				Withdrawal Assessments[y]	Long-Term Follow-up [z]
	Month					
	13	14	15	Q2M After Month 15		
Eligibility Verification (Inclusion/ Exclusion Criteria)	X[d]					
Symptom Directed Physical Exam and Medical Assessment[f]	X	X	X	X	X	X
Weight, Height and BMI[g]					X	
Waist Circumference					X	
Hip Circumference					X	
Vital Signs (BP, HR, Temperature)[h]					X	
12-lead ECG[i]					X	
HIV Associated Conditions	X	X	X	X	X	X
AEs, SAEs, Concomitant Medications	X	X	X	X	X	X
ISR Assessment for IM injection		X	X	X	X	X
Clinical chemistry and Hematology	X	X	X	X	X	X
Pregnancy Testing[l]	S	U	U	U	S	U
HIV-1 RNA and sample for storage (S)[m]	X	X	X	X	X	X
CD4+ cell count		X	X	X	X	X
CD8+ cell count					X	
Urinalysis[n]		X			X	
Fasting Labs Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides[o]		X			X	
Whole Blood (Virology)					X	
CCI						
PBMCs [q]					X	

Procedure	Extension Phase				Withdrawal Assessments[y]	Long-Term Follow-up [z]
	Month					
	13	14	15	Q2M After Month 15		
PK sampling [u] (S)=Storage only		S	S		X	S
Oral CAB and Oral RPV Dispensation [v]	X					
IP accountability (Pill Counts)	X	X				
IM treatment administration [w]		X	X	X		
Reason for Switch[cc,ee]	X					

Time and Events Table for BIK to Direct to Injection – Extension Phase:

Procedure	Extension Phase			Withdrawal Assessments[y]	Long-Term Follow-up [z]
	Month				
	13	14	Q2M After Month 14		
Eligibility Verification (Inclusion/ Exclusion Criteria)	X[d]				
Symptom Directed Physical Exam and Medical Assessment[f]	X	X	X	X	X
Weight, Height and BMI[g]				X	
Waist Circumference				X	
Hip Circumference				X	
Vital Signs (BP, HR, Temperature)[h]				X	

Procedure	Extension Phase			Withdrawal Assessments[y]	Long-Term Follow-up [z]
	Month				
	13	14	Q2M After Month 14		
12-lead ECG[i]				X	
HIV Associated Conditions	X	X	X	X	X
AEs, SAEs, Concomitant Medications	X	X	X	X	X
ISR Assessment for IM injection	X	X	X	X	X
Clinical chemistry and Hematology	X	X	X	X	X
Pregnancy Testing[l]	S	U	U	S	U
HIV-1 RNA and sample for storage (S)[m]	X	X	X	X	X
CD4+ cell count		X	X	X	X
CD8+ cell count				X	
Urinalysis[n]		X		X	
Fasting Labs Glucose, Cholesterol (Total, HDL and LDL) and Triglycerides[o]		X		X	
Whole Blood (Virology)				X	
CCI					
PBMCs [q]				X	
PK sampling [u] (S)=Storage only		S		X	S
IP accountability (Pill Counts)	X				
IM treatment administration [w]	X	X	X		
Reason for Switch[cc,ee]	X				

Safety Follow Up Visit: Conduct approximately 4 weeks after the last dose of IP. Required only if the participant has ongoing AEs or lab abnormalities at the last on-study visit. This visit may be conducted by telephone.

Note: BP – Blood pressure, HR – Heart Rate, BMI – Body Mass Index, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, PT - Prothrombin Time, PTT - Partial Thromboplastin Time, INR - International normalized ratio, PBMC – peripheral blood mononuclear cell, RNA – Ribonucleic acid, HbA1c = Glycated hemoglobin, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1.

a. Complete all Screening assessments within 35 days. Participants may begin the Maintenance Phase as soon as all Screening assessments are complete. Participants may be rescreened once and will be assigned a new participant number.
b. For participants who elect to participate in the oral lead in period, oral CAB 30 mg + RPV 25 mg will be administered and the oral lead will start on Day 1. For participants who choose to go directly into injections, the first loading dose will be administered on Day 1. Visits for participants on the BIK arm are expected to occur every 56 days as projected according to the Day 1 visit. There is a ±3 day visit window, from the projected visit date (Maintenance Phase of the study).
c. For participants who elect to participate in the oral lead in period, the first loading dose will be administered and the oral lead in will end. For participants who choose to go directly into injections, the second loading dose will be administered.
d. Confirmation of eligibility to continue the Maintenance Phase, and eligibility to enter the Extension Phase.
e. Collect full routine medical history plus (report at Baseline visit): HIV risk factors (may be collected at a later study visit), cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal, bone, and neurologic disorders. At Month 11 (D2I)/12 (OLI and BIK), assessments inclusive of smoking status, alcohol use and illicit drug use since the start of the study will be administered.
f. Physical exams should be conducted as part of normal routine clinical care. Medical assessments include any decisions the study staff must make for participants management and/or care of participant.
g. Height collected at Baseline Day 1 only. Recommended procedures to measure weight, waist and hip circumference can be found in Section 10.10. Weight related measurements to be collected are weight, body fat %, total body water %, muscle mass, and bone mineral mass.
h. Measure vital signs after about 5 minutes of rest in a semi-supine position.
i. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes. ECGs will be performed pre-dose. ECG pre-dose will be performed in triplicate at Day 1. A 2-hour post-dose ECG will also be performed at Day 1 (D2I), Month 1 (OLI) and Month 12 (OLI)/Month 11 (D2I) for participants receiving CAB LA + RPV LA with an allowable window of ± 30 minutes.
j. Only SAEs related to study participation or to a concomitantly administered ViiV/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
k. On Day 1, the eC-SSRS is to be administered prior to randomization. The eC-SSRS will be completed at the beginning of the visit following administration of other PROs required prior to injections. The eC-SSRS is not required during the Withdrawal visit if withdrawal occurs during the Extension Phase.
l. Women of childbearing potential only. S=serum, U=urine. Pregnancy events will be captured starting at Day 1 following initial exposure to study drug. Serum pregnancy test can substitute for urine pregnancy test if locally required but must be appropriately timed to confirm pregnancy status prior to randomization and first IM administration. If the urine test is positive, perform a serum test and do not administer injection. The frequency of pregnancy tests should be performed according to local legal requirements.
m. Month 12 (OLI and BIK) and Month 11 (D2I) HIV-1 RNA retest (within 4 weeks) for results > 50 c/mL will be captured as unscheduled visit. Plasma for storage samples will be used for possible future analyses.
n. A morning specimen is preferred. To assess biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; urine phosphate; beta-2-microglobulin; and retinol binding protein.
o. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
p. Only collect if the Withdrawal visit occurs at Month 6 or Month 12 (OLI and BIK); Month 5 or Month 11 (D2I).
q. Whole blood/PBMC collection samples may be used for virologic analyses. PBMCs will be collected at baseline Day 1, Month 6, Month 12, or Withdrawal if prior to Month 12 (OLI and BIK). PBMCs will be collected at baseline Day 1, Month 5, Month 11, or Withdrawal if prior to Month 11 (D2I)
r. Blood sample for insulin, HbA1c, and renal and bone biomarker assessments: **Renal:** CystatinC; Beta-2-Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type 1-N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D.

s. CCI [redacted]

t. Informed consent for genetic research must be obtained before sample collection. Sample may be collected at any visit after signing informed consent, but preferably at the Day 1 visit.

u. **One blood sample for CAB and RPV each to be collected at each PK timepoint**. At Month 1, for participants who elected to participate in the Oral Lead in, and Month 14 for participants who were randomized to BIK and switched to CAB LA + RPV LA in the Extension Phase and will participate in the Oral Lead in, Pre dose PK samples are to be collected: PRIOR to the final oral dose of CAB + RPV. **For pregnant participants** (on CAB+RPV arm): two blood samples for CAB and one RPV sample at each PK timepoint. Refer to Section 10.6.6.3.

v. Participants who elected to participate in the Oral Lead in before switching to CAB LA + RPV LA injections, will take final dose of oral lead-in regimen in the clinic at the Month 1/Month 14 visit and begin injections.

w. If possible, injections should be spaced approximately 2 cm from one another and from the site of any previous injection and or any injection site reaction. Bring RPV LA to approximately room temperature prior to injecting. Time and location of injection (right or left) as well as needle length used will be collected in the eCRF. The first injection can be performed before central lab results become available and safety parameters are reviewed.

x. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Months 6 and 12 (OLI and BIK); Month 5 and 11 (D2I).

y. Refer to Section 7.1 of the protocol for additional information on performing withdrawal assessments

z. Participants receiving one or more injections with CAB LA and/or RPV LA will be assessed with clinic visits at Months 3, 6, 9 and 12 during the Long-Term Follow-Up Phase

aa. BIK dispensation (1-month supply) for participants who plan on entering into the Extension Phase. Participants who do not enter the Extension Phase or do not wish to transition to the commercial supply will not receive 1-month supply at M12.

bb. Data from visit will be used to determine participant's eligibility to enter the Extension Phase of study. If participant elects to enter the Extension Phase, determine if the participant will elect to start injections immediately or start with oral lead in.

cc. All PROs are recommended to be administered before other assessments and injections take place at each designated visit.

dd. Only collected if Withdrawal visit occurs during the Maintenance Phase.

ee. Will be administered only to participants randomized to BIK, successfully completing the Maintenance Phase and deciding to enter Extension Phase and switching to CAB LA + RPV LA.

ff. When assessing CDC stage at Screening/Baseline, consider only the latest available CD4 T-cell count, except when the participant had an active Stage 3 event 6 months prior to Screening.

gg. At Month 11 (D2I)/ Month 12 (OLI or BIK) or withdrawal, (depending which is sooner) participants will be asked if any cosmetic procedures were performed during the conduct of the study.

2. INTRODUCTION

The current paradigm in the treatment of Human Immunodeficiency Virus (HIV) involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires additional improvements on the durability, safety and tolerability, and convenience of all antiretroviral classes. Fixed-dose combinations (FDCs) have greatly advanced HIV treatment by allowing simplification of dosing and reducing pill burden. However, adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Among regimens of comparable efficacy, physicians and HIV-1-infected patients who receive ART rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Drug resistant virus eventually emerges in most patients who struggle with consistent adherence. Different HIV treatment modalities are being developed to help improve adherence and patient outcomes and prevent resistance and transmission of the virus.

There is also an increasing desire to develop nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens for long-term treatment of HIV infection as an approach to avoid known NRTI-associated adverse drug reactions and long-term toxicities. In addition, simplifying treatment has long been a goal to increase treatment compliance and improve the quality of life for patients with HIV.

Cabotegravir (CAB) is a potent integrase inhibitor that possesses attributes that allow formulation and delivery as a long-acting (LA) parenteral product. Rilpivirine (RPV) 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. RPV is a globally marketed product available as oral 25 mg tablets [Edurant Product Information, 2019], and is also formulated as a LA product. Intramuscular administration of a two-drug combination therapy with CAB LA plus RPV LA may offer a better tolerability and resistance profile, as well as improved adherence and treatment satisfaction in virologically suppressed patients.

2.1. Study Rationale

The overall objective of the CAB LA + RPV LA clinical development program is to develop a highly effective, well tolerated two drug long-acting injectable regimen which has the potential to offer improved treatment convenience, compliance and improved quality of life for individuals with HIV compared to current standard of care. Week 160 efficacy (GSK data from study 200056 (LATTE-2)) [GlaxoSmithKline Document Number 2018N380094_00, 2019] demonstrated that 90% of patients randomized to the CAB LA + RPV LA Q8W dosing arm and 83% of patients randomized to the Q4W dosing arm maintained virologic suppression (HIV-1 RNA <50 c/mL), with both regimens being well tolerated. In study 207966 (ATLAS-2M), 1.7% of participants in the CAB + RPV Q8W group and 1.0% of participants in the CAB + RPV Q4W group met the primary efficacy endpoint of plasma HIV-1 RNA ≥50◦c/mL at Week◦48. In both studies, both regimens were well tolerated, and the results justify further evaluation of both CAB LA + RPV LA dosing regimens.

The current study, 213500 (**SOLAR – S**witch **O**nto **L**ong **A**cting **R**egimen) is designed to demonstrate the non-inferior antiviral activity of CAB LA 600 mg + RPV LA 900 mg administered every 2 months (Q2M) compared to Biktarvy (BIK) administered orally once daily for 12 months. The study will also provide important comparative antiviral activity, safety, tolerability of these regimens through Month 12 of the Maintenance Phase of the study. Additionally, eligible participants (HIV-1 RNA <50 c/mL at Month 12) will be given an option to continue their randomized CAB LA + RPV LA regimen (Q2M) or start CAB LA + RPV LA Q2M after 12 months of oral therapy in the Extension Phase of the study.

2.1.1. Optional Oral Lead In

Throughout the course of the clinical development program for CAB and RPV LA including the large P3 trials of FLAIR, ATLAS and ATLAS 2M, an oral lead-in phase of cabotegravir (30 mg) along with rilpivirine (25mg), administered daily for 30 days, was an integral component of these trials and allowed for a safety assessment before study participants were allowed to advance to the LA phase of these studies. As a result, all study participants underwent a one-month period of oral dosing with CAB/RPV followed by an evaluation of safety labs, and if labs were within normal limits, participants were allowed to transition into LA dosing.

An assessment of the safety data specific to four weeks of oral lead-in for participants on FLAIR and ATLAS (ViiV's two registrational clinical trials) was recently undertaken and as a result of the accumulated safety data which has been generated, the safety of oral CAB and RPV during these four weeks of oral lead-in was not significantly different than at any other time during the FLAIR/ATLAS studies. The SOLAR study will also allow an optional oral lead in for participants randomized to the LA arm of SOLAR. This decision to dose with or without an oral-lead-in will be determined by the study participant following informed consent discussions with the investigator.

2.1.2. Weight Gain

Weight gain in people living with HIV is multifactorial with both traditional (diet, exercise, concomitant medications such as selective serotonin reuptake inhibitor and others) and HIV specific modifiable risks likely contributing factors. Which factor or factors are most significant in the pathogenesis of weight gain in HIV disease has not been fully elucidated.

Whereas lipodystrophy involved accumulation of central abdominal or visceral fat, and loss of subcutaneous fat, weight gain in HIV-infected individuals receiving newer, more recently approved antiretroviral treatment consists of general fat gain – both subcutaneous and central fat – with an increase in waist circumference. Weight gain among HIV-infected individuals often occurs after the initiation of antiretroviral therapy with certain antiretrovirals linked more closely to weight gain than others. Teasing out what is considered appropriate weight gain for individuals returning back to health versus what is consider more pathogenic weight gain has been challenging. Recent studies have demonstrated increase weight gain with integrase strand transfer inhibitor (INSTI)-based regimens compared to other classes of antiretroviral therapy [Bourgi, 2019; Kerchberger, 2019; McComsey, 2019]. Moreover, additional components of the antiretroviral regimen,

specifically the nucleoside reverse transcriptase inhibitor TAF has also been associated with excess weight gain [McCann, 2019]. Women and non-whites appear to be most at risk.

Lipohypertrophy, an abnormal accumulation of visceral fat and/or ectopic fat depots, continues to be a problem for individuals with HIV infection, but the role that INSTIs plays in this metabolic alteration has not been fully elucidated. Moreover, weight gain and anthropometric changes in body composition in HIV disease is poorly understood but may lead to or exacerbate pre-existing comorbidities including cardiovascular disease and diabetes [Debroy, 2019; Hill, 2020]. Given the evolving nature of this issue, it is important to determine the impact that INSTI has on weight gain in the SOLAR study; if there are differences in weight gain between different types of integrase inhibitors and the role that TAF, in particular, plays on accentuating weight gain. The SOLAR study will allow an assessment of weight changes between participants continuing on an orally administered bictegravir based regimen (Biktarvy) compared to participants switching to an IM administered, integrase inhibitor, cabotegravir. Finally, the impact of TAF on weight changes will also be assessed in this study.

Another important outcome that will be measured as an assessment in the SOLAR study is the impact between Biktarvy versus LA CAB/RPV on contributing to the metabolic alterations that have been associated with ARV therapy and that leads to the metabolic syndrome. Classically, metabolic syndrome is a cluster of conditions that occurs together increasing one's risk of heart disease, stroke and type 2 DM. These conditions include increased BP, elevated blood glucose levels, excess body fat around the waist and abnormal fasting cholesterol and TG levels. The defining levels for each characteristic of metabolic syndrome are listed below (Table 1) (Grundy, 2004).

Table 1 ATP III Clinical Identification of Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference[a, b]	
Men	≥102 cm (≥40 in)
Women	≥88 cm (≥35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL[c]

a. Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated BMI. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

b. Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, eg, 94 to 102 cm (37 to 39 inch). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

c. The American Diabetes Association has recently established a cutpoint of 100 mg/dL, above which persons have

either prediabetes (impaired fasting glucose) or diabetes. This new cutpoint should be applicable for identifying the lower boundary to define an elevated glucose as one criterion for metabolic syndrome.

Additionally, non-alcoholic fatty liver disease (steatosis) is increasingly associated with chronic liver disease and diabetes and is an important contributor to insulin resistance and metabolic syndrome. Features of steatosis include hepatocellular injury, inflammation and fibrosis. The fibrosis-4 score (FIB-4) is a simple, non-invasive test to determine the degree of hepatic fibrosis. The FIB-4 score combines standard biochemical values (ALT, AST, platelets), and age into a simple formula that estimates the amount of scarring in the liver.

Fibrosis 4 Score Formula:

$$(\text{Age} \times \text{AST}) / (\text{Platelets} \times (\sqrt{\text{ALT}}))$$

In a previous study, A FIB-4 index < 1.45 had a negative predictive value of 94.7% to exclude severe fibrosis with a sensitivity of 74.3%. A FIB-4 index > 3.25 had a positive predictive value to confirm the existence of significant fibrosis (F3-4) of 82.1% with a specificity of 98.2% [Vallet-Pichar, 2007]

Therefore, this study will explore whether there is a meaningful difference between these two regimens with respect to alterations in BP, blood glucose and cholesterol (and TG) levels, and whether there are changes in hip and waist circumferences in participants randomized to continue with Biktarvy versus those who are randomized to switch to LA CAB/RPV.

2.2. Background

It is estimated that 37.9 million people are currently living with HIV/Acquired Immunodeficiency Syndrome (AIDS) and that the worldwide epidemic continues to grow at a rate of 1.7 million new infections and cause 770, 000 deaths per year [UNAIDS, 2019]. Chronic HIV infection in adults continues to be characterized by increased development of resistant virus, increasing transmission of resistant virus and issues associated with long term toxicity of ART. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires a need for continuous improvement on the durability, tolerability and convenience of all antiretroviral classes.

A study by the Antiretroviral Therapy Cohort Collaboration [ART-CC, 2013] found that of more than 21,000 patients in a European and North American cohort on their first combination antiretroviral therapy (cART) regimen (either PI or NNRTI-based), 51% modified or interrupted their first cART regimen during a median of 28 months of follow-up with one third of interruptions occurring within the first 6 months of starting therapy. Forty percent of all treatment interruptions were due to the secondary side effects or toxicities of cART, 17% were due to the desire for simplification of the regimen and 14% were due to patient choice. These observations have led to numerous "switch" ART studies, designed to understand the efficacy, safety, and tolerability of switching patients from one regimen to another.

Previous studies have evaluated switches to ritonavir-boosted PI monotherapy in virologically suppressed patients [Bierman, 2009 and Arribas, 2012]. These studies suggest that simplifying from a three-drug dual class regimen to a single boosted protease inhibitor may be a safe and effective option for the majority of participants studied, who have effectively maintained viral suppression. In the OLE study, virologically suppressed (HIV-1 RNA <50 c/mL) HIV-1 infected participants receiving a lopinavir-ritonavir (LPV/r) + lamivudine (3TC) or emtricitabine (FTC) based NRTI regimen simplified to a dual regimen of LPV/r + 3TC or FTC. In a modified Intent-to-Treat (m-ITT) analysis, dual therapy with LPV/r + 3TC demonstrated non-inferiority efficacy and comparable safety to LPV/r + 2 NRTIs [Arribas, 2015].

CAB LA + RPV LA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV.

Three Phase IIb studies (LAI116482 [LATTE], 200056 [LATTE-2], and 209035 [POLAR]) have been conducted with oral CAB and/or IM CAB LA, evaluating an induction/maintenance simplification approach. Three Phase III studies (201584 [FLAIR], 201585 [ATLAS], and 207966 [ATLAS-2M]) conducted with CAB LA + RPV LA are ongoing. Details of these studies can be found in the CAB IB [GlaxoSmithKline Document Number RPS-CLIN-004375, 2021].

Biktarvy (BIK) is a three-drug combination of bictegravir (BIC), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIK. Clinical trial results of studies with BIK can be found in Biktarvy Prescribing Information, 2019.

Long-acting 2-class therapy consisting of CAB LA + RPV LA as an IM regimen has the benefit of being a NRTI-sparing regimen for long-term treatment of HIV infection which will avoid known NRTI-associated adverse drug reactions and long-term toxicities. Additionally, a 2-drug combination therapy with CAB LA plus RPV LA may offer a better tolerability and resistance profile, as well as improved adherence and treatment satisfaction in virologically suppressed participants improving the quality of life for people living with HIV.

2.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with oral and CAB LA or RPV LA can be found in the Investigator's Brochures [GlaxoSmithKline Document Number RPS-CLIN-004375, 2021; RPV IB, 2021].

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

2.3.1. Risk Assessment

Oral CAB and CAB LA (GSK1265744/GSK1265744 LA)

Since CAB exposure in humans with or without HIV infection is limited, the clinical safety profile in humans has yet to be fully elucidated. The following risks have primarily been identified during routine preclinical testing and/or from the clinical trial experience to date and are considered of potential relevance to clinical usage in the context of this protocol. Additional information about the clinical experience to date and possible risks associated with treatment using CAB can be found in the Summary of Data and Guidance for the Investigator section of the IB [GlaxoSmithKline Document Number RPS-CLIN-004375, 2021].

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 have developed transaminitis (elevated liver transaminases characterised by predominant alanine aminotransferase (ALT) elevation). In most participants, transient transaminitis was explained by acute viral hepatitis infection (majority). 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. An optional 4-week oral lead- in is being implemented in this study, where participants can choose to receive oral CAB prior to the administration of IM CAB to assess individual tolerability	• Exclusion criteria as described in Section 5.2 will prohibit participants with significant liver impairment based on screening liver chemistry including transaminases (ALT and Aspartate aminotransferase [AST]) as well on prior medical history. Participants with a history of chronic liver disease with ongoing inflammation and/or fibrosis will have additional confirmatory assessments to confirm suitability for entry into the study. • Liver transaminases (ALT and AST) will be monitored throughout this study (refer to SoA, Section 1.3) and the liver chemistry stopping criteria will be adopted as described in Section 7.1.2.1 of this protocol. Participants will be withdrawn from CAB treatment where no compelling alternative cause is identified, and DILI is suspected.
Injection Site Reactions (ISRs)	Clinical, experience to date has demonstrated ISRs occur in the majority of exposed participants treated with CAB LA but are generally CCI (Grade 1) or CCI (Grade 2)	• Administration advice will be given to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and include events of pain, tenderness, erythema, or nodule formation of several days' duration (median duration for individual events <1 week). ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well tolerated and have not to date been associated with an excess of participants withdrawing.	treatment of ISRs is given in study documentation • Advice will be given to participants on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate. • Participants will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. • Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored
Hypersensitivity Reactions (HSR)	Hypersensitivity reactions have been reported as uncommon occurrences with integrase inhibitors, including the closely related compound dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. While there have been no clinical cases of hypersensitivity to CAB to date, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic	• The potential risk of developing a hypersensitivity reaction post administration of IM CAB may be minimized by the use of a 4-week oral lead-in of oral CAB to determine individual safety and tolerability prior to the introduction of IM CAB if the participant is randomized to CAB LA administration and chooses to participate in the oral lead in. • Clinical assessments, laboratory tests (including

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	liver transaminases) and vital signs will be performed throughout this study (refer to Schedule of Activities, Section 1.3). Results from these assessments may aid early detection of HSR. • Oral CAB will be withdrawn immediately for participants with suspected HSR during the oral CAB lead-in phase and they would not proceed to the injection phase. Participants in the injection phase would not receive further injections. During oral and IM CAB treatment, any HSR reactions that occur would be managed supportively.
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. A delay in the onset of parturition, increased stillbirths and neonatal deaths were observed in a rat pre- and postnatal development study at greater than 30 times the exposure at the	• Pregnant females are excluded from enrolment in this study and women of childbearing potential (WOCBP) 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. • WOCBP are also required to undergo regular pregnancy testing throughout study conduct. Pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	recommended human dose (RHD). No evidence of adverse developmental outcomes was observed with oral cabotegravir in rats or rabbits (greater than 30 times or similar to [approximately 0.7] times the exposure at the RHD, respectively) given during organogenesis. The clinical significance of these findings in humans is unknown. For pregnant participants remaining in the study, refer to Appendix 6 for additional data regarding CAB and pregnancy.	• Participants who become pregnant during the study may remain in the study provided all protocol defined pregnancy related assessments, procedures and documentation are completed, and a pregnancy specific informed consent form (ICF) addendum is signed by the participant. Details regarding management of pregnant participants are found in Appendix 6
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 (NTDs) 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 NTD, out of 2,824 women. A causal relationship of these events to the use of DTG has not been established. The incidence of NTDs in the general population ranges from 0.5-1 cases per 1,000 live births. As NTDs occur within the first	• Pregnant females are excluded from enrolment in clinical trials of CAB at this time and women of childbearing potential (WOCBP) are required to adopt highly reliable means of contraception during participation and throughout the long term follow up phase of the studies after exposure to CAB LA. • WOCBP also undergo regular pregnancy testing throughout study conduct. Pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy. It should be noted that CAB concentration could remain for prolonged

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. Recently updated data (April 2020) for this birth outcome study showed that among women who were on DTG when they became pregnant, 7/3591 NTD occurred (0.19%). In comparison, NTDs were identified in 21/19,361 (0.11%) women delivering on any non-DTG antiretrovirals. There was not a significant difference in the number of NTDs between births to women taking DTG and those taking other non-DTG antiretroviral treatments (0.09% difference). The clinical relevance of either of these findings in relation to CAB use is unknown.	periods despite discontinuation of CAB LA. • Participants who become pregnant during the study may remain in the study, provided that all protocol defined pregnancy related assessments, procedures and documentation are completed and a pregnancy specific ICF addendum is signed by the participant. Details regarding management of pregnant participants is found in Appendix 6.
Development of Resistance following discontinuation of CAB LA	Residual concentrations of CAB would remain in the systemic circulation for prolonged periods (more than 1 year in some cases) in participants who stop CAB LA treatment, (e.g., for tolerability issues or treatment failure). Participants discontinuing CAB LA regimen may therefore be at risk for developing HIV-1 resistance to CAB after discontinuing injectable therapy.	• After participants stop CAB LA, Oral HAART regimens will be prescribed within 8 weeks after the last Q2M dose, and following consultation with the medical monitor. This would be anticipated to result in continued suppression or rapid resuppression of HIV-1 RNA thus minimizing the risk of emergent resistance • The participants in this study who discontinue IM CAB for any reason will be monitored for a

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		minimum of 52 weeks from the time of the last IM CAB injection.
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for CAB and CAB LA, refer to Section 6.11 CAB and CAB LA should not be co-administered with the following medicinal products, as significant decreases in CAB plasma concentrations may occur (due to UGT enzyme induction), which may result in loss of therapeutic effect of CAB. - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin - the antimycobacterials rifampicin, rifapentine, rifabutin - St John's wort (Hypericum perforatum) Oral CAB administration only: Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB. Participants discontinuing a LA regimen may be at risk for developing DDIs many weeks after	• All participants will be informed of prohibited medications throughout the study and updates provided as needed via the informed consent.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
	discontinuing injectable therapy.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that CAB LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher than expected concentrations of CAB shortly after injection and lower concentrations thereafter. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of overdose with CAB LA are currently unknown. HIV-1 viral suppression may not be effective following accidental maladministration.	• Training will be provided to all sites on proper injection technique. • Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose electrocardiogram (ECG), vital signs, or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor will be notified. • Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all participants. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB concentrations.

ORAL RPV

For safety and risk mitigation for oral RPV refer to the RPV local prescribing information [Edurant Product Information, 2021].

RPV LA

Information about the clinical experience to date and possible risks associated with treatment using RPV LA can be found in the Summary of Data and Guidance for the Investigator section of the IB [RPV IB, 2021]. Systemic reactions following RPV LA injections have been observed in clinical trials. These occur infrequently (in less than 0.5% of participants) and typically begin to resolve within minutes of the injection, some participants have required supportive care. Where PK data was available, high RPV PK plasma concentrations have been observed which may have resulted from an accidental partial IV injection of RPV. The following risks are considered to be of specific clinical relevance in the context of IM use.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Injection Site Reactions	Clinical, experience to date has demonstrated ISRs occur in the majority of exposed participants treated with RPV LA but are generally CCI (Grade 1) or CCI (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days' duration (median duration for individual events <1 week). ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well tolerated and have not to date been associated with an excess of participants' withdrawal due to ISRs. None of the ISRs was serious and no clinically significant complications were reported	• Administration advice to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and treatment of ISRs given in study documentation. • Advice to participants on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate. • Participants will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. • Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored • Significant ISRs may be photographed and referred to a dermatologist for specialist advice.
Rash	Some observations of rash with oral RPV have been reported in clinical studies executed to date (the majority are Grade 1 or 2). Severe skin and hypersensitivity reactions have been reported during the postmarketing experience, including cases of Drug Reaction with	• In this study, for participants who are randomized for RPV LA administration and choose to participate in the optional oral lead in will be preceded by an oral RPV lead in to evaluate safety and tolerability in individual participants. • Participants with a Grade 1 or 2 rash will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Eosinophilia and Systemic Symptoms (DRESS), with oral RPV containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries.	allowed to continue treatment, depending on the clinical judgment of the investigator. • All participants experiencing a Grade 3 or 4 rash should discontinue their ARV medication (study medication) 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. See Section 8.3.11.9 for additional guidance on management of rash events.

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

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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	discontinuing injectable therapy.	
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that RPV LA can be inadvertently administered intravenously instead of intramuscularly possibly resulting in higher than expected concentrations of RPV shortly after injection and lower concentrations thereafter. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. In addition, HIV-1 viral suppression may not be effective following accidental intravenous maladministration.	• Training will be provided to all sites on proper injection technique. • Should IM maladministration be suspected at any time (e.g., suspected under or overdose or inadvertent IV dosing), post dose ECG monitoring and vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified • Laboratory samples for safety parameters and HIV-1 RNA will be closely monitored in all participants. Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of RPV concentrations.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Other Study Related Risks		
Venipuncture	Participants will be required to have blood samples taken. Risk of bruising, and rarely, infection	• Trained personnel will perform venipuncture
Risks of ECG pad removal	Participants will be required to have ECG tracings recorded periodically throughout the study Some discomfort and rash may occur where the ECG pads are removed.	• ECGs will be conducted by appropriately trained personnel and effort made to minimize contact time for application of the pads.
Risk of Treatment Failure	This study employs a novel 2 drug LA ART maintenance regimen for the treatment of HIV-1 infection that remains experimental. Both IM CAB and RPV have demonstrated antiviral activity in large clinical studies and the two-drug combination has demonstrated sustained antiviral activity in studies, LAI116482, 200056, 201584, 201585 and 207966. Doses of the CAB LA and RPV LA have been selected to achieve exposures that are expected to maintain virologic efficacy on the basis of available data with the oral and LA formulations. Due to administration error, it is possible that a participant could receive an inadequate dose of CAB LA or RPV LA. Sub-therapeutic concentrations of either CAB LA or RPV LA	• Viral loads and CD4+ cell counts will be closely monitored throughout the study (maintenance and extension phases), allowing for early detection of failing treatment. Where confirmed virological failure occurs, participants would be discontinued from study drugs and transferred to an oral HAART regimen. • Plasma samples will be collected and stored throughout the Maintenance Phase for potential determination of CAB and RPV concentrations and possible pharmacokinetic correlation with virologic response.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	could lead to virologic failure and possibly the development of viral resistance.	

Biktarvy (BIK)

For safety and risk mitigation for BIK, refer to the BIK product information [Biktarvy Product Information, 2019].

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV	Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of BIK.	• All chronic HBV infected patients (HBsAg+ are excluded from study as are those who are negative for anti-HBs but positive for anti-HBc (negative HBsAg status) AND positive for HBV DNA are also excluded from study. • Patients coinfected with HIV-1 and HBV who discontinue BIK should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions	The concomitant use of BIK with certain other drugs may result in known or potentially significant drug interactions, some of which may lead to (See Section 6.11.1): • Loss of therapeutic effect of BIK and possible development of resistance. • Possible clinically significant adverse reactions from greater exposures of concomitant drugs. Consider the potential for drug interactions prior to and during BIK therapy;	• See BIK product information for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. • Monitor for the adverse reactions associated with the concomitant drugs.
New Onset or Worsening Renal Impairment	Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials of BIK, there have been no cases of Fanconi syndrome or Proximal Renal Tubulopathy (PRT). In clinical trials of BIK in participants with no antiretroviral treatment history with eGFRs greater than 30 mL per minute, and in virologically suppressed participants switched to BIK with eGFRs greater than 50 mL per minute, renal serious adverse events were encountered in less than 1% of participants treated with BIK through Week 48 (see Biktarvy Product Information, 2019). Patients taking tenofovir prodrugs who have	• During treatment with BIK, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. • In patients with chronic kidney disease assess serum phosphorus. • Discontinue BIK in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions. Prior to or when initiating BIK, and during treatment with BIK, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue BIK in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.	
Lactic Acidosis/Severe Hepatomegaly with Steatosis	Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of BIK, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals.	• Treatment with BIK should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

2.3.2. Benefit Assessment

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

Participants receiving CAB LA + RPV LA are anticipated to benefit from maintenance of virological suppression using LA agents. The regimen provides an alternative to daily oral treatment with an extended dosing option, avoiding drug-drug and drug-food interactions within the GI tract with IM dosing. Participants randomized to receive CAB LA+ RPV LA Q2M dosing will not need to take concomitant daily oral therapy. Adherence in these participants is expected to be improved and will be directly observed during IM injections. Efficacy of the two-drug regimen, as oral agents, has been demonstrated through Week 312 of the LAI116482 study, and as IM agents, has been demonstrated through Week 160 of the ongoing 200056 study and Week 48 of the ongoing ATLAS 2M study. The reduction in ART, and the discontinuation of NRTIs, may offer long term safety and tolerability benefits in these participants.

2.3.3. Overall Benefit: Risk Conclusion

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

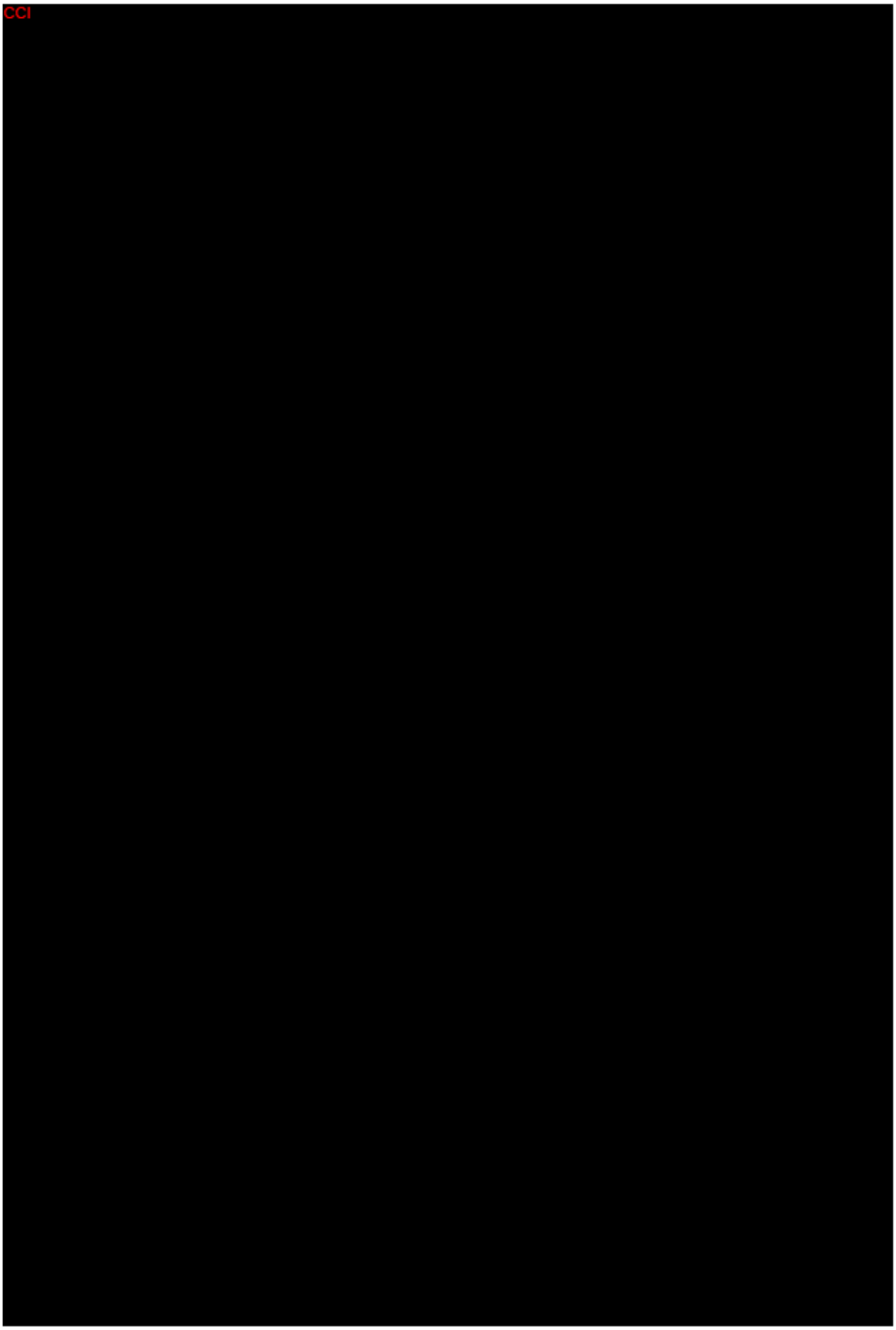
3. OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
To demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every two months compared to a BIK single tablet regimen administered once daily over 12 months in suppressed HIV-1 infected antiretroviral therapy (ART)-experienced participants	Proportion of participants with plasma HIV-RNA greater than or equal to 50 copies/mL as per Food and Drug Administration (FDA) Snapshot algorithm at Month 12 (OLI and BIK)/Month 11 (D2I) (Intent-to-Treat Exposed [ITT-E] population)
Secondary	
To demonstrate the antiviral and immunologic response with the use of CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen administered once daily	Proportion of participants with plasma HIV-1 RNA <50 c/mL (c/mL) at Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I) using the FDA Snapshot algorithm (Intent-to-Treat Exposed [ITT-E] population)

Objectives	Endpoints
	Proportion of participants with protocol-defined confirmed virologic failure (CVF) through Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I). Proportion of participants with HIV-RNA greater than or equal to 50 c/mL as per FDA Snapshot algorithm at Month 6, and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I) Absolute values and changes from Baseline in viral load and CD4+ cell count over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I)
To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, BIC, FTC, and TAF through Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in participants treated with CAB LA + RPV LA compared to BIK	Change from Baseline (Day 1) in renal and bone biomarkers at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I).
To evaluate Metabolic Syndrome for participants treated with CAB + RPV and BIK	Change from Baseline in proportions of participants with Metabolic syndrome at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I)
To evaluate insulin resistance in participants treated with CAB LA + RPV LA compared to BIK	Change from Baseline (Day 1) in homeostasis model of assessment-insulin resistance (HOMA-IR) at Months 6 and 12 (OLI and BIK)/Month 5 and Month 11 (D2I).
To assess preference for CAB LA + RPV LA administered every 2 months compared to a BIK single tablet regimen administered once daily	Preference for CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen will be assessed using a preference questionnaire at Month 12 (OLI)/Month 11 (D2I) (or Withdrawal).

Objectives	Endpoints
To assess patient reported treatment satisfaction, and injection tolerability.	Change from baseline (Day 1) in total "treatment satisfaction" score, and individual item scores of the HIV Treatment Satisfaction Status Questionnaire (HIVTSQs) at Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I), (or Withdrawal) Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire HIVTSQc total score and individual item scores at Month 12 (OLI and BIK)/Month 11 (D2I) (or Withdrawal). Change from Month 2 in Dimension scores ("Acceptance of ISRs", "Bother of ISRs", "Leg movement", "Sleep") and individual item scores (assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time) will be assessed using the Perception of injection questionnaire (PIN) at Months 2, 6, and 12 (OLI)/Months 1, 5, 11 (D2I) (or Withdrawal)
Safety	
To evaluate the safety and tolerability of CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen administered once daily	Incidence and severity of AEs and laboratory abnormalities over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I). Proportion of participants who discontinue treatment due to AEs over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I). Change from Baseline in laboratory parameters over time including Month 6 and Month 12 (OLI and BIK)/Month 5 and Month 11 (D2I).
CCI [redacted]	

CCI



4. STUDY DESIGN

4.1. Overall Design

213500 (**SOLAR** – Switch **O**nto **L**ong **A**cting **R**egimen) is a Phase IIIb, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of a two-drug regimen of CAB LA + RPV LA administered every 2 months compared with maintenance of BIK. Approximately 654 adult HIV-1 infected patients who are on the stable ARV regimen BIK will be randomized 2:1 to either be switched to the CAB LA + RPV LA regimen or continue current ART through 12 months. The study will continue with an Extension Phase after Month 12 (OLI and BIK)/Month 11 (D2I).

Participants will be randomized (2:1) at Day 1 to either discontinue BIK and either choose to begin oral therapy with CAB 30 mg + RPV 25 mg once daily to determine individual tolerability, prior to administration of CAB LA + RPV LA, or transition directly to injections, or continue on BIK. Current ART dosing on Day 1 is not

recommended to occur after randomization to avoid overlap of regimens (in the event that the participant is assigned to the CAB LA + RPV LA treatment arm). However, if the participant takes BIK prior to coming into the clinic, randomization and initiation of oral CAB and RPV or injections should continue as planned for Day 1.

For those randomized to receive CAB + RPV and choose to begin the oral lead in, at the Month 1 visit, safety assessments (including e.g., clinical chemistries) will be performed as per the SoA (Section 1.3). At visit Month 1, participants will return to the clinic, take the last dose of oral CAB + RPV, and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). The first injection visit (Month 1) can be performed before central lab results are available and safety parameters are reviewed. If a retest is required based on Month 1 labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Month 1). Those participants who choose to start injections immediately will receive the first CAB LA (600 mg) + RPV LA (900 mg) injections on Day 1.

Randomization will be stratified by gender at birth and BMI. The primary endpoint for the study is the proportion of participants with plasma HIV-1 RNA ≥50 c/mL who meet the ≥50 c/mL criteria at Month 12. The proportion of participants with plasma HIV-1 RNA <50 c/mL at Month 12 using the FDA Snapshot algorithm (Missing, Switch or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] population) is a key secondary endpoint.

A total of 654 participants with a 2:1 randomization ratio to either CAB LA+RPV LA or BIK is such that the study has approximately 85% power to demonstrate non-inferiority in the proportion of participants with snapshot virologic failure at Month 12 using a 4% margin, assuming a true 2% failure rate for CAB LA + RPV LA and a 1% failure rate for the BIK arm using a 2.5% one-sided alpha level. The randomized portion of the study will continue for 12 months with an Extension Phase.

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during this study, except those allowed and defined in the protocol. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the SoA (Section 1.3), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be communicated promptly to the study medical monitor.

4.1.1. Screening Phase (up to 35 days)

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

Participants will complete a screening period of up to 35 days. A single repeat of a procedure/lab parameter is allowed to determine eligibility (unless otherwise specified). In exceptional circumstances only, if a repeat lab is required because a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor for consideration of participant eligibility. A repeat central lab will be submitted concurrently or at the next planned visit. Participants may be re-screened once which

requires a new participant number. Participants who are randomized into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may be randomized as soon as all eligibility requirements have been confirmed at the site.

4.1.2. Maintenance Phase

At Day 1, eligible participants will be randomized 2:1 to either the CAB LA + RPV LA Q2M arm or the BIK arm. For participants who are randomized to the CAB LA + RPV LA arm, they will be able to choose to begin oral therapy with CAB 30 mg + RPV 25 mg once daily to determine individual safety and tolerability, prior to administration of CAB LA + RPV LA or transition directly to injections:

Oral Lead In

Participants will remain on oral BIK until the Day 1 visit, and until any required Screening visit retest results are available for review. On Day 1, participants who choose to participate in the oral lead in will be administered oral CAB 30 mg + RPV 25 mg once daily for one month (participants will be assessed for tolerability after one month). At Month 1, participants will have the assessments completed as per the SoA (Section 1.3.), including clinical chemistries. The participant will take the last dose of oral CAB + RPV, and to receive the first CAB LA + RPV LA injections (within 2 hours of the final oral dose). The first injection visit with IM CAB LA 600 mg and RPV LA 900 mg can be performed before central lab results are available and safety parameters are reviewed. The second IM injection with CAB LA 600 mg and RPV LA 900 mg will be performed at Month 2 with a visit window of -7 days allowed. **Receiving LA dosing up to +7 days is not recommended and the Medical Monitor must be contacted**. Subsequent injections with CAB LA 600 mg and RPV LA 900 mg will occur every 2 months thereafter, from the projected visit date, with a dosing window of ±7 days allowed If the injection is expected to fall outside of the dosing window, the Medical Monitor must be contacted to discuss individual participant case management.

Direct to Inject (no oral lead-in)

Central lab results (or local lab results if a central lab is not available) and safety parameters from the Screening visit must be available and reviewed for participants who choose to transition directly to injections without an oral lead-in. Participants with ongoing safety issues or laboratory abnormalities of clinical concern (e.g. Grade 3 or Grade 4 liver chemistry elevations) will require consultation and agreement with the Medical Monitor prior to proceeding directly to injections in the Maintenance Phase. If a clinical chemistry retest is required based on Screening visit labs, the retest should be performed as soon as possible (and preferably no later than 7 days following the Screening visit). Participants will remain on BIK until the Day 1 injection visit, and until any required Screening visit retest results are available for review.

At Day 1, eligible participants will take the last dose of BIK and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg) as initial loading doses. Clinical chemistries will also be obtained at Day 1. The second and third injections (CAB LA 600 mg + RPV LA 900 mg) will be administered at Month 1 and Month 3. The second IM injection with CAB LA 600 mg and RPV LA 900 mg will be performed at Month 1 with a visit window of -7-days . For the second IM injection, a visit window for **LA dosing from +1 to +7 days is not recommended and the Medical Monitor must be contacted** before the second IM injection is given. Subsequent injections (CAB LA 600 mg + RPV LA 900 mg) will occur every 2 months thereafter, from the projected visit date, with a ±7-day dosing window being allowed. If the injection is expected to fall outside of the dosing window, the Medical Monitor must be contacted to discuss individual participant case management.

Note: ***Study participants with ≥Grade 1 ALT at screening and or Day 1 must be discussed with the Medical Monitor prior to initiation of LA dosing; continuation in the study or progression onto LA dosing may require additional evaluations, including labs drawn after a period of oral dosing with CAB + RPV.***

BIK

Continue on current ART (BIK) regimen for 12 months. Participants who successfully complete Month 12 (without meeting study defined withdrawal criteria and who remain virologically suppressed (HIV-1 RNA <50 c/mL) will be given the option to switch to the LA arm in the Extension Phase (with or without an OLI) or to successfully complete and withdraw from the study (no withdrawal visit needed).

4.1.3. Extension Phase

All eligible participants who transition into the Extension Phase will continue study treatment until CAB LA and RPV LA are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur every 2 months.

Participants not eligible to enter the Extension Phase will end their study participation. Sites may be reimbursed for up to a one-month supply of antiretroviral medication to facilitate transition to non-study ART for participants that do not qualify for the Extension Phase.

NOTE: the transition plan to marketed product (either CAB+RPV LA or alternative HAART) should be done in consultation with the Central Study Team and the Medical Monitor. Participants with ongoing safety issues or laboratory abnormalities of clinical concern (e.g. Grade 3 or Grade 4 liver chemistry elevations) will require consultation and agreement with the Medical Monitor prior to proceeding to commercial supply.

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

All participants who successfully complete 12 months of CAB LA + RPV LA treatment in the Maintenance Phase will continue to have access to both CAB LA and RPV LA in the Extension Phase. See the SoA (Section 1.3) for more information.

4.1.3.2. Participants Entering from the BIK Arm

Participants randomized to continue BIK will have the option to either continue study participation by switching to CAB LA + RPV LA in the Extension Phase, or to complete their study participation at Month 12 (no withdrawal visit needed). The transition from BIK to CAB LA + RPV LA within the Extension Phase can be completed with or without an oral lead-in prior to commencement of injectable treatment. The participant's decision will be taken in consultation with the investigator and must be appropriately documented. As participants approach the Month 13 visit, sites must ensure sufficient CAB and RPV supply are available to support the participant's decision for transition to LA.

Participants who choose to continue on to the Extension Phase will need to be assessed for eligibility to begin the CAB LA + RPV LA regimen. Participants will continue on BIK while eligibility is being confirmed.

All participants with an undetectable HIV-1 RNA (<50 c/mL) result from the Month 12 visit are eligible to enter the Extension Phase. A single repeat of HIV-1 RNA for any participant with a HIV-1 RNA ≥50 c/mL and < 400 c/mL at Month 12 must be performed. The retest should be scheduled as soon as possible (but no later than 4 weeks from the Month 12 visit). Participants with a HIV-1 RNA <50 c/mL upon retest are eligible to enter the Extension Phase. Participants with HIV-1 RNA ≥400 c/mL at Month 12 are not eligible to enter the Extension Phase, will not be allowed a repeat to determine eligibility, and will therefore be withdrawn from the study.

Result of HIV-1 RNA at Month 12	**Action**
<50 c/mL	Begin Extension Phase for participants randomized to BIK at Month 13
≥50 c/mL but <400 c/mL	Perform HIV-1 RNA retest as soon as possible (not later than 4 weeks).
Single repeat <50 c/mL	Begin Extension Phase for participants randomized to BIK at Month 13
Single repeat ≥50 c/mL	Cannot begin Extension Phase and must be withdrawn from study; Complete withdrawal visit
≥400 c/mL	Cannot begin Extension Phase and must be withdrawn from study; Complete withdrawal visit.

Please refer to Section 6.11.1 for a list of prohibited medications concurrent with either formulation for CAB and/or RPV.

Participants Transitioning Direct to Injection in the Extension Phase:

Central lab results (or local lab results if a central lab is not available) and safety parameters from the Month 12 visit must be available and reviewed for participants who choose to transition directly to injections. Participants with ongoing safety issues or laboratory abnormalities of clinical concern (e.g. Grade 3 or Grade 4 liver chemistry elevations) will require consultation and agreement with the Medical Monitor prior to proceeding directly to injections in the Extension Phase.

If a clinical chemistry retest is required based on Month 12 labs, the retest should be performed as soon as possible (and preferably no later than 7 days following Month 12). Participants will remain on oral BIK until the Month 13 injection visit, and until any required Month 12 retest results are available for review.

At Month 13, eligible participants will take the last dose of BIK and receive the first injections of CAB LA (600 mg) + RPV LA (900 mg) as initial loading doses. Clinical chemistries and safety assessments will also be obtained at Month 13. The second injection (CAB LA 600 mg + RPV LA 900 mg) will be administered at Month 14, with a visit window of -7-days . **Receiving LA dosing from +1 to +7 days is not recommended and the Medical Monitor must be contacted before the next injection is given**. Subsequent injections (CAB LA 600 mg + RPV LA 900 mg) will occur every 2 months thereafter, from the projected visit date, with a ±7-day dosing window being

allowed. If the injection is expected to fall outside of the dosing window, the Medical Monitor must be contacted to discuss individual participant case management.

Participants Receiving Optional Oral Lead-In in the Extension Phase:

As participants approach the Month 13 visit, sites must ensure sufficient oral CAB and RPV are available for participants who choose to use the oral lead-in.

At Month 13, eligible participants who after discussion with the investigator, choose to receive the optional oral lead-in will initiate a 4-week lead-in of oral CAB 30 mg + oral RPV 25 mg once daily. It is not necessary to dose BIK on the day the participant begins the oral lead-in with CAB + RPV. However, if the participant takes BIK prior to coming into the clinic, initiation of oral CAB and RPV should continue as planned. Clinical chemistries will be assessed at Month 13. At Month 14, following the 4-week CAB + RPV oral lead-in, participants will have additional safety assessments including clinical chemistries as per the SoA (Section 1.3). At the Month 14 visit, participants will take the last dose of oral CAB + RPV and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + RPV). The first injections can be performed before central lab results become available and safety parameters are reviewed. The second injection (CAB LA 600 mg + RPV LA 900 mg) will be administered at Month 15 with a - 7-day window being allowed. **Receiving LA dosing up to +7 days is not recommended and the Medical Monitor must be contacted**. Subsequent injections (CAB LA 600 mg + RPV LA 900 mg) will occur every 2 months (bi-monthly) thereafter, from the projected visit date, with a ±7-day dosing window being allowed. If the injection is expected to fall outside of the dosing window, the Medical Monitor must be contacted to discuss individual participant case management.

4.1.4. LTFU Phase – IM Regimen Only

Any participant who receives at least one dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. **Investigators must discuss the choice of the follow-up HAART regimen with the Medical Monitor prior to initiating the new regimen with the participant. HAART therapy should be initiated within 8 weeks (± 7 days) after the last Q2M injection.** The LTFU will begin the day of the last CAB LA and/or RPV LA dose and continue for 52 weeks, or until the assigned CAB LA + RPV LA regimen is locally approved and commercially available. These participants will complete Withdrawal assessments and will then enter into the LTFU as per the Time and Events Schedule. In addition, for participants who withdraw during the LTFU, the final visit will be considered the study withdrawal visit.

After receiving at least one dose of LA CAB and LA RPV, participants who decide to no longer continue with LA dosing for whatever reason must transition to the 52 week long term follow up (LTFU) phase of SOLAR. These participants are considered on study but off IP and should return for follow up visits at 3, 6, 9 and 12 months after the last LA was administered.Female participants of child bearing potential must continue to use adequate

contraception methods (see Study Procedures Manual for list of accepted forms of contraception) for the entire year of follow up.

In order to assure that participants have access to HAART during the LTFU, ViiV may supply HAART regionally or reimbursement will be provided as needed during this phase. The LTFU Phase may be shortened or terminated at any time during the study for various reasons, e.g., better understanding of risks of development of resistance as CAB and RPV exposures decline, regulatory approval and commercial availability, end of study timings, etc. If the participant is administered an ABC-containing product, see Section 8.3.11.8.

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

Participants who are randomized to LA CAB and LA RPV and chose to perform the Oral Lead In and decide not to continue while performing the Oral Lead in are not required to enter the LTFU.

4.1.5. Independent Data Monitoring Committee

Given the well-established safety and efficacy data for CAB and RPV LA from multiple prior studies including LATTE-2, ATLAS, FLAIR, and ATLAS-2M, coupled with a well characterized safety profile of the comparator arm (BIK), the SOLAR study team in consultation with the ViiV Safety and Labeling Committee (VSLC) decided that no formal IDMC or iSRC is warranted for this study.

Furthermore, accumulating study data from this study will be regularly reviewed in aggregate by the CAB Safety Review Team (SRT). Any new, emerging safety signals detected by the SRT will be acted upon by the study team. An interim analysis is planned to review primary and secondary efficacy data and key safety data when all participant complete Month 6 visit. These actions will provide comprehensive data monitoring for the study in the absence of IDMC.

4.2. Type and Number of Participants

The target population to be enrolled is HIV-1 infected, virologically suppressed (HIV-1 RNA <50 c/mL) participants on a BIK single tablet regimen.

It is anticipated that approximately 654 participants will be enrolled into SOLAR. A 15% screen failure rate is anticipated. Participants will be enrolled from multiple countries including (but not limited to) Canada, UK, Ireland, France, Germany, Spain, Italy, Switzerland, Austria, Netherlands, Belgium, Japan, Australia, and the United States.

Randomization will be stratified by gender at birth and BMI. A goal of this study is to enroll populations who are underrepresented in clinical studies, including approximately

20% women. Sites are expected to take into account gender in their screening strategies in order to achieve women enrolment. .

4.3. Scientific Rationale for Study Design

The design of this study (2:1 randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study) is well established for confirming the non-inferiority of an investigational agent compared with an active comparator and is generally accepted by regulatory authorities as rigorous proof of antiviral activity. The primary endpoint, proportion of participants defined as virologic failures by the FDA Snapshot algorithm is recommended in the FDA's 2015 guidance document [CDER, 2015] for assessing efficacy in Switch Trials. The key secondary endpoints, proportion with plasma HIV-1 RNA <50 c/mL at Month 6 and Month 12, is also a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression. The Extension Phase will allow for a collection of longer-term efficacy, safety and tolerability data for the CAB LA + RPV LA Q2M regimen.

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

The 200056 (LATTE-2) [GlaxoSmithKline Document Number 2013N168152_09, 2017] and the ATLAS-2M [GlaxoSmithKline Document Number 2017N326521_02, 2018] clinical trials evaluated a different simplification approach and served as proof of concept for this study. In 200056, HIV-1 RNA suppression was induced with a three-drug antiretroviral regimen consisting of CAB + ABC/3TC FDC, and then participants switched to a two-drug two-class regimen consisting of CAB LA + RPV LA for the maintenance of HIV-1 RNA suppression. Results demonstrate that through 96 weeks on two-drug maintenance therapy, 94% (Q8W IM arm) and 87% (Q4W IM) of participants maintained virologic suppression (HIV-1 RNA <50 c/mL) compared to 84% of participants continuing oral CAB + 2 NRTIs. CAB LA + RPV LA was well tolerated through Week 96 for both the Q8W and Q4W dosing regimens, as demonstrated by a low discontinuation rate due to AEs, including injection site reaction (ISR) related AEs in either dosing arm, with no significant dose-dependent trends in safety parameters. On the basis of 200056 Week 48, and Week 96 data, Q4W and Q8W IM dosing are being progressed into Phase 3 for further clinical development, respectively. In 207966, 1.7% of participants in the CAB + RPV Q8W group and 1.0% of participants in the CAB + RPV Q4W group met the primary efficacy endpoint of plasma HIV-1 RNA ≥50◦c/mL at Week◦48. Based on a 4% non-inferiority margin, CAB◦+◦RPV Q8W is non-inferior to CAB + RPV Q4W at Week◦48 because the upper bound of the 95% CI for the adjusted treatment difference [0.8 (-0.6, 2.2)] is less than 4%.

The open-label design for 213500 (SOLAR) best suits the objectives of this study. A double-blind, double-dummy design for this study would result in an increased pill burden in all participants, a requirement for placebo injections across the comparator arms, elevated risk of oral ART non-adherence in participants receiving placebo injections, limitations to patient reported preference data comparing injectable and oral ART, as well as considerable trial design complexities. A blinded design is also complicated by the requirement for an oral lead-in, in participants who elect to receive this short-term regimen at the start of study before the initiation of CAB LA + RPV LA injections. Blinding the oral lead-in would require additional placebo pills for 5 weeks in the ART continuation arm, that otherwise would not be required. This study utilizes a 2:1 randomization that provides advantages with respect to costs, gathering additional safety information, reduces the effect of any learning curves due to injection administration or metabolic testing and improves recruitment.

In addition to study design challenges, the impact of blinding carries the potential risk of oral regimen non-compliance, in participants on the ART continuation arm, who may believe that they are receiving active drug via injection (and therefore possibly increased risk of HIV transmission to uninfected partners). The additional risk of inadvertent non-adherence to oral ART outweighs any benefits that may be gained through a blinded design.

Importantly, a key objective for the planned Phase 3 studies is to understand the acceptability and patient reported preferences to this novel injectable regimen, relative to daily oral standard of care (SOC) ART. An unblinded study design supports collection of participant preference data in a way that would not be possible if a double-blind, double-dummy design were implemented. Due to the complexities, limitations and risks of blinding, this study is planned as an open label study.

To maintain the integrity of the trial, data aggregated by actual treatment group will not be made available to members of the Study Team and will not be shared with Investigators until the primary analysis at Month 12. In addition, central stratified randomization will be used to ensure that selection bias is avoided (see Section 6.2). The stratification factors gender and BMI will be considered based on historical studies. Lastly, ascertainment bias affecting the primary efficacy analysis is unlikely since the primary endpoint is inherently objective, being primarily determined by HIV-1 RNA laboratory assessment. The open label design should therefore have no impact on the analysis of study endpoints.

4.3.1. Participant Input into Design

Participants were not involved in the design of the clinical trial.

4.4. Justification for Dose

4.4.1. CAB + RPV

4.4.1.1. CAB and RPV Pharmacokinetics Following Q8W and Q4W Dosing

In pivotal Phase 3 studies 201585 and 201584 (ATLAS and FLAIR, CAB LA 400 mg + RPV LA 600 mg Q4W demonstrated non-inferiority to oral standard of care. In the Phase 3b Study 207966 (ATLAS 2M), CAB LA 600 mg + RPV LA 900 mg Q8W was non-inferior to the Q4W regimen while achieving lower overall trough concentrations. Participants naïve to CAB+RPV received CAB LA 600 mg + RPV LA 900 mg initiation injections at Week 4b (following a 4-week oral lead-in) and second (first continuation) injections at Week 8 regardless of regimen. Select trough concentrations following Q8W and Q4W dosing in ATLAS 2M are summarized in Table 2.

Table 2 Summary of Evaluable Plasma CAB and RPV Trough Concentrations by Regimen at Select Visits for Participants with No Prior Exposure to CAB + RPV (Study 207966, ATLAS 2M)

Visit	Plasma CAB (µg/mL)				Plasma RPV (ng/mL)			
	n	Q8W (n=326)	n	Q4W (n=326)	n	Q8W (n=326)	n	Q4W (n=326)
Week 4b[b]	282	5.18 [4.93, 5.45] (45)	292	5.29 [5.04, 5.55] (43)	283	77.2 [72.8 ,81.9] (54)	292	78.3 [73.6, 83.3] (58)
Week 8[c]	273	1.57 [1.46, 1.69] (67)	267	1.52 [1.40, 1.64] (74)	272	48.2 [45.3, 51.2] (54)	267	45.5 [42.7, 48.4] (56)
Week 16	262	1.41 [1.32, 1.51] (58)	253	2.13 [2.02, 2.25] (46)	260	46.2 [44.0, 48.5] (41)	252	57.8 [54.6, 61.2] (49)
Week 24	219	1.44 [1.34, 1.56] (62)	228	2.41 [2.29, 2.54] (41)	220	49.5 [46.8, 52.3] (44)	228	63.4 [60.1, 67.0] (44)
Week 48	217	1.58 [1.49, 1.68] (47)	236	2.71 [2.58, 2.84] (39)	217	65.4 [61.9, 69.1] (43)	235	89.3 [84.5, 94.2] (44)

Data Source: 207966 CSR Table 4.5. GlaxoSmithKline Document Number 2019N406358_00, 2019]

a. Geometric mean [95% CI] (CVb%).

b. Represents trough at the end of 1-month oral lead-in prior to initiation injections.

c. Represents trough 4-weeks following CAB 600 mg and RPV 900 mg initiation injections prior to first continuation injections.

4.4.1.2. Q8W versus Every 2 Month Dosing

Separate population PK models for CAB LA and RPV LA that included concentration data from Phase 3 studies were developed and validated [GlaxoSmithKline Document Number 2019N421460_00, 2019 and GlaxoSmithKline Document Number EDMS-ERI-198151177, 2019]. Simulations (including oral lead in) were performed to compare the impact of changing from Q8W (7 doses/year 1) to every other month dosing (6.5 doses/ year 1). Differences between predicted trough concentrations following Q8W and every 2-month dosing are considered minimal (Figure 1, Figure 2).

Figure 1 Comparison of CAB LA Q8W and Every 2 Months

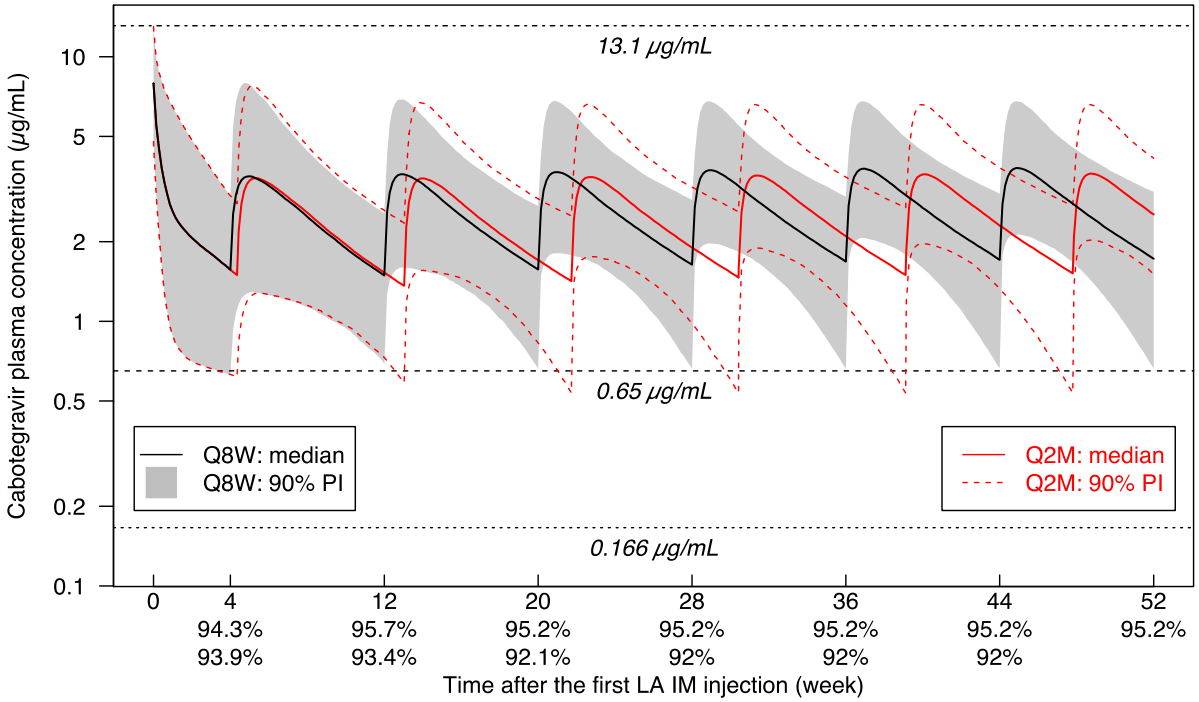
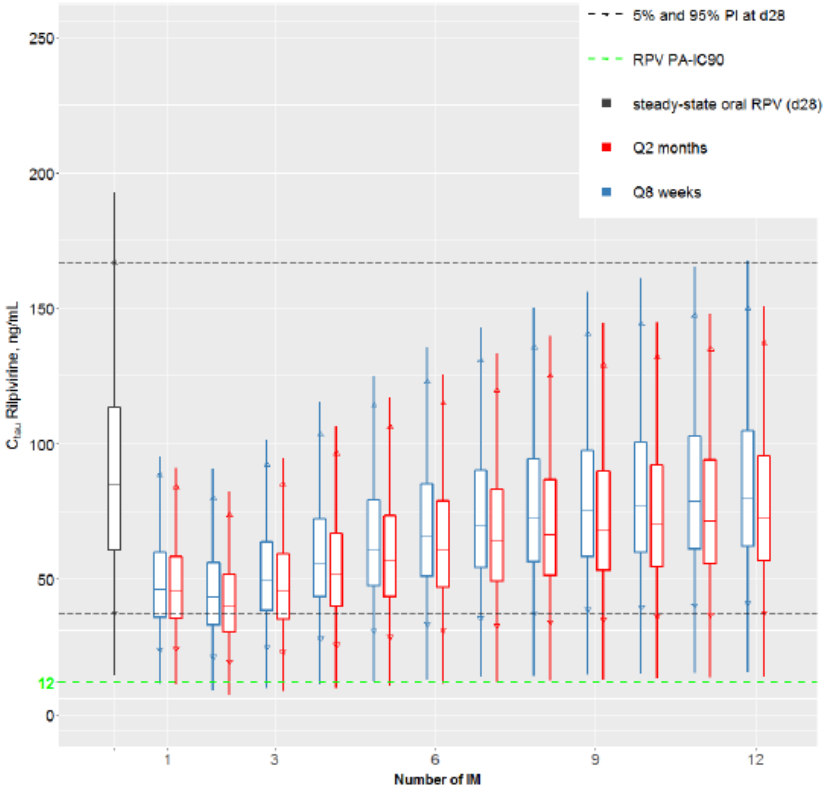


Figure 2 Comparison of RPV LA Q8W and Every 2 Months



C_{tau}, trough concentration; IM, intramuscular; LA, long acting; Q8W, every 8 weeks, RPV, rilpivirine.

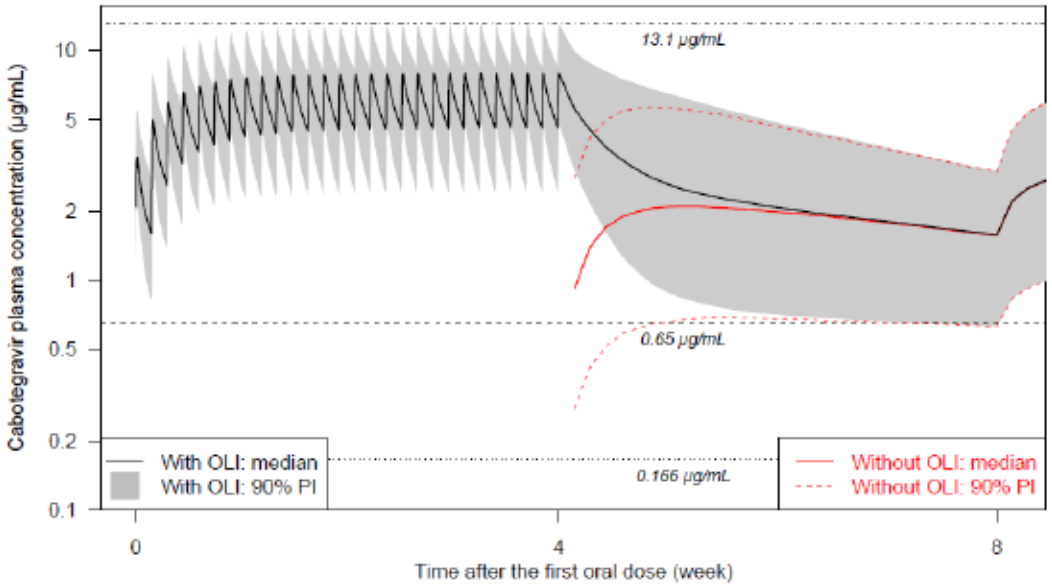
For 1-week delays in dosing median CAB and RPV troughs decrease ~10% with 99% of participants predicted to have troughs above respective PA-IC90 values.

4.4.1.3. Optional Oral lead-in

The purpose of the oral lead-in is to assess the individual participant tolerability of CAB and RPV prior to administration of the prolonged release suspension injections. The impact of the oral lead-in on the CAB LA and RPV LA PK profiles is limited and it is not required for the achievement of either therapeutic or steady-state dose levels. In addition, participants are virologically suppressed upon initiation of CAB LA + RPV LA injections and will receive continuing contribution of the prior oral regimen to the overall antiviral activity if stopped the same day as initiation injections. Plasma concentrations at the end of the first dosing interval (4 weeks after injection) are similar with or without the prior oral lead-in (Figure 3, Figure 4). CCI [redacted]

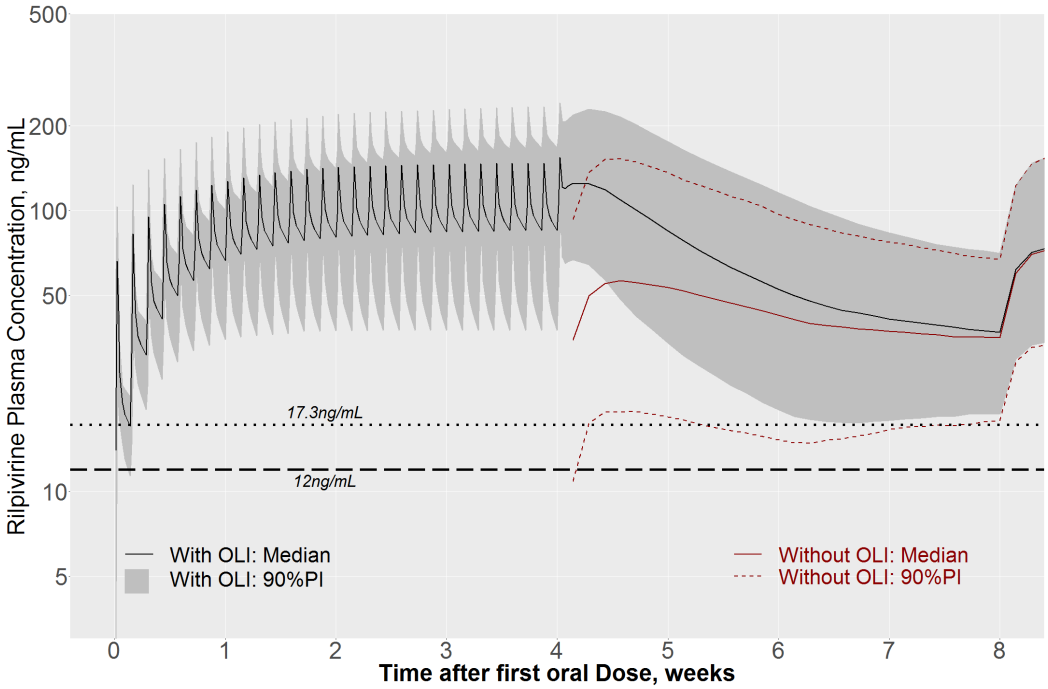
Participants opting to receive oral lead-in dosing will receive CAB 30 mg + RPV 25 mg once daily with food during the first month of the study.

Figure 3 Simulated Median (90% PI) CAB Concentration-Time Profiles for CAB LA 600 mg Initiation Injection with and without OLI



Reference lines: 0.166 µg/mL=PA-IC90; 0.65µg/mL=5th percentile predicted W8 trough following initiation injections in FLAIR and ATLAS; 13.1µg/mL= median Cmax following CAB 60 mg PO QD observed in LATTE

Figure 4 Simulated Median (90% PI) RPV Concentration-Time Profiles for RPV LA 900 mg Initiation Injection with and without OLI



4.4.2. BIC/FTC/TAF (BIK)

BIK will be administered as the marketed three-drug fixed dose combination product containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF orally once daily with or without food in adults.

4.5. End of Study Definition

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

Study Completion

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

- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including Month 11/12 (with or without Month 11/12 study treatment) and did not enter the Extension Phase;
- Randomly assigned to either treatment group, completed the randomized Maintenance Phase including Month 11/12, and entered and completed the Extension Phase (defined as remaining on study until commercial supplies of the CAB LA + RPV LA Q8W regimen become locally available or development of CAB LA + RPV LA is terminated).

An safety Follow-Up visit will be conducted approximately 4 weeks after the last dose of study medication for participants with ongoing AEs, and serious adverse events (SAEs) and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit. Assessments at the safety Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality). Safety Follow-Up visits are not required for successful completion of the study and can be in clinic or conducted by phone.

5. STUDY POPULATION

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational regimen or other study treatment that may impact participant eligibility is provided in the current IBs for CAB [GlaxoSmithKline Document Number RPS-CLIN-004375, 2021 and RPV IB, 2021], Edurant Prescribing Information, 2021 and Biktarvy prescribing information, 2019.

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

5.1. Inclusion Criteria

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

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

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

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

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

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

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

The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

INFORMED CONSENT

3. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Eligible participants or their legal guardians (and next of kin when locally required), must sign a written Informed Consent Form before any protocol-specified assessments are conducted. Enrolment of participants who are unable to provide direct informed consent is optional and will be based on local legal/regulatory requirements and site feasibility to conduct protocol procedures.

OTHER

4. Participants enrolled in France must be affiliated to, or a beneficiary of, a social security category.

5. Must be on the uninterrupted current regimen of BIK for at least 6 months prior to Screening with an undetectable HIV-1 viral load for at least 6 months prior to Screening. BIK must be the participant's first or second regimen. If BIK is the second regimen, the first regimen must be an INI regimen. Any history of non-INSTI regimens (ie. NNRTI, PI, C-C chemokine receptor type 5 [CCR5] and other entry inhibitors) are not permitted. Any prior change in regimen, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done for treatment failure (HIV-1 RNA ≥400 c/mL).

   The following are limited exceptions:

   - A change from TDF to TAF will not be considered a regimen change.
   - Historical perinatal use of an NRTI when given in addition to an ongoing HAART will not be considered a change in ART regimen.
   - The past use of ARVs in the context of PEP or PrEP while the patient was HIV negative will be allowed. Such cases will be evaluated on a case by case basis with the Medical Monitor, and may require documentation of HIV negative serology during time of PEP or PrEP
   - A change in dosing scheme of the same drug from twice daily to once daily will not be considered a change in ART regimen if data support similar exposures and efficacy.
   - A change in formulation from multiple class regimens to single treatment regimens (of the same medications) would not be considered a change in ART regimen.

6. Documented evidence of plasma HIV-1 RNA measurements <50 c/mL in the 6 months prior to Screening .

7. Plasma HIV-1 RNA <50 c/mL at Screening.

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

5.2. Exclusion Criteria

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

Exclusionary Criteria prior to Screening or Day 1

1. Within 6 months prior to Screening, any plasma HIV-1 RNA measurement ≥50 c/mL

2. Within the 6 to 12-month window prior to Screening, documented evidence of any plasma HIV-1 RNA measurement >200 c/mL, or 2 or more plasma HIV-1 RNA measurements ≥50 c/mL. NOTE: This statement does not apply to study participants who started treatment within the 6 to 12-month window prior to screening.

3. History of prior treatment failure to any DHHS recommended ART regimen.

4. History of drug holiday >1 month for any reason prior to Screening visit, except where all ART was stopped due to tolerability and/or safety concerns

5. Any change to a second line regimen, defined as change of a single drug or multiple drugs simultaneously, due to virologic failure to therapy (defined as a confirmed plasma HIV-1 RNA measurement ≥200 c/mL after initial suppression to <50 c/mL while on first line HIV therapy regimen)

6. Participants who are currently participating in or anticipate being selected for any other interventional study.

Exclusionary medical conditions- for all participants

7. Women who are pregnant, breastfeeding or plan to become pregnant or breastfeed during the study

8. Any evidence of a current Center for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring

systemic therapy, and CD4+ counts <200 cells/μL are not exclusionary.

9. Participants with moderate to severe hepatic impairment
10. Any pre-existing physical or mental condition (including substance use disorder) which, in the opinion of the Investigator, may interfere with the participant's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participant
11. Participants determined by the Investigator to have a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder. A participant with a prior history of seizure may be considered for enrolment if the Investigator believes the risk of seizure recurrence is low. All cases of prior seizure history should be discussed with the Medical Monitor prior to enrolment
12. All participants will be screened for syphilis.
    - Participants with untreated secondary (late latent) or tertiary syphilis infection, defined as a positive RPR and a positive treponemal test without clear documentation of treatment, are excluded.
    - Participants with a false positive RPR (with negative treponemal test) or serofast RPR result (persistence of a reactive nontreponemal syphilis test despite history of adequate therapy and no evidence of re-exposure) may enroll after consultation with the Medical Monitor.
    - Participants with primary syphilis or early latent secondary syphilis (acquired within the preceding year) who have a positive RPR test and have not been treated may be treated during the screening period and if completion of antibiotic treatment occurs during the screening period, may be allowed entry after consultation with the Medical Monitor. If antibiotic treatment cannot be completed before the screening window ends, participants may be rescreened once following completion of antibiotic therapy for primary or early latent secondary syphilis.
13. Participants who, in the investigator's judgment, pose a significant suicide risk. Participant's recent history of suicidal behavior and/or suicidal ideation should be considered when evaluating for suicide risk
14. The participant has a tattoo, gluteal implant/enhancements or other dermatological condition overlying the gluteus region which may interfere with interpretation of injection site reactions
15. Evidence of Hepatitis B virus (HBV) infection based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs) and HBV DNA as follows:
    a. Participants positive for HBsAg are excluded;
    b. Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status), whether negative or positive for HBV DNA, are excluded

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

16. Asymptomatic individuals with chronic hepatitis C virus (HCV) infection will not be excluded, however Investigators must carefully assess if therapy specific for HCV infection is required; participants who require or qualify for immediate HCV treatment are excluded (see Section 5.3.1 for those co-infected participants who post entry into SOLAR decide treatment for HCV infection is warranted or desired either by the participant or by the treating physician.

    Participants with HCV co-infection will be allowed entry into this study if:

    a. Liver enzymes meet entry criteria

    b. HCV Disease has undergone appropriate work-up, and is not advanced, and will not require treatment prior to the Month 14 visit. Additional information (where available) on participants with HCV co-infection at screening should include results from any liver biopsy, Fibroscan, ultrasound, or other fibrosis evaluation, history of cirrhosis or other decompensated liver disease, prior treatment, and timing/plan for HCV treatment.

    c. In the event that recent biopsy or imaging data is not available or inconclusive, the Fib-4 score will be used to verify eligibility

        i. Fib-4 score >3.25 is exclusionary

        ii. Fib-4 scores 1.45 – 3.25 requires Medical Monitor consultation

        Fibrosis 4 Score Formula:

        (Age x AST) / (Platelets x (sqr [ALT])

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

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

19. Ongoing or clinically relevant pancreatitis

20. Clinically significant cardiovascular disease, as defined by history/evidence of congestive heart failure, symptomatic arrhythmia, angina/ischemia, coronary artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) or any clinically significant cardiac disease

21. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the Study medical monitor for inclusion of the participant prior to randomization

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

23. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class. In addition, if heparin is used during PK sampling, participants with a history of sensitivity to heparin or heparin-induced thrombocytopenia must not be enrolled
24. Current or anticipated need for chronic anti-coagulation with the exception of the use of low dose acetylsalicylic acid (≤325 mg) or hereditary coagulation and platelet disorders such as haemophilia or Von Willebrand Disease.
25. Corrected QT interval (QTc (Bazett)) >450 msec or QTc (Bazett) >480 msec for participants with bundle branch block.
26. Known or suspected active COVID-19 infection OR has had contact with an individual with known COVID-19, within 14 days of study enrolment.

Exclusionary Laboratory Values or Clinical Assessments at Screening (a single repeat to determine eligibility is allowed)

27. Known or suspected presence of resistance mutations as defined by the IAS-USA resistance guidelines [IAS-USA, 2019] to the individual components of BIK (BIC, FTC, TAF), RPV, and CAB by any historical resistance test result.

    Note: Prior genotypic resistance testing (genotyping of plasma vRNA and/or PBMC vDNA) is not required but if available it must be provided to ViiV, after screening and before randomization according to guidance in the SPM, to provide direct evidence of no pre-existing exclusionary resistance mutations. You must wait for the study virologists to confirm the lack of exclusionary resistance mutations, which will be provided before the screening window closes. Details regarding baseline or prior resistance data must be noted in the source documentation
28. Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening phase to verify a result
29. Any acute laboratory abnormality at Screening, which, in the opinion of the investigator, would preclude the participant's participation in the study of an investigational compound
30. Participant has estimated creatine clearance <30mL/min per 1.73m^2 via Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) Method
31. Alanine aminotransferase (ALT) ≥3 × ULN

Concomitant Medications
32. Exposure to an experimental drug or experimental vaccine within either 30 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to Day 1 of this study; 33. Treatment with any of the following agents within 28 days of Screening: • radiation therapy; • cytotoxic chemotherapeutic agents; • tuberculosis therapy with the exception of isoniazid (isonicotinylhydrazid, INH); • anti-coagulation agents; • Immunomodulators that alter immune responses such as chronic systemic corticosteroids, interleukins, or interferons. Note: Participants using short-term (e.g. ≤21 days) systemic corticosteroid treatment; topical, inhaled and intranasal corticosteroids are eligible for enrolment. 34. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening 35. Treatment with any agent, except recognized ART as allowed above, with documented activity against HIV-1 within 28 days of study Day 1. Treatment with acyclovir/valacyclovir is permitted. 36. Use of medications which are associated with Torsade de Pointes. (See SPM for a list of relevant medications) 37. Participants receiving any prohibited medication and who are unwilling or unable to switch to an alternate medication. Note: Any prohibited medications that decrease CAB, RPV, BIC, FTC or TAF concentrations should be discontinued for a minimum of four weeks or a minimum of three half-lives (whichever is longer) prior to the first dose and any other prohibited medications should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose

5.3. Additional Eligibility Criteria

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

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

5.3.1. HIV/HCV Treatment Considerations for Co-infected Participants

For participants who decide to initiate HCV treatment at any point while on study, either secondary to newly acquired acute HCV infection or, if a change in treatment strategy for those who entered the study HIV/HCV co-infected, such participants may be permitted during the Maintenance Phase before the primary endpoint is reached but would require consultation with and approval by the Medical Monitor to commence HCV therapy. The choice of HCV direct acting antiviral agents being considered must be HCV regimens endorsed by DHHS guidelines with minimal drug-drug interactions as detailed in the most current DHHS HIV treatment guidelines.

5.4. Screening/Baseline/Run-in Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events.

A single repeat of a procedure / lab parameter is allowed to determine eligibility (unless otherwise specified).

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

5.5. Lifestyle Considerations

5.5.1. Meals and Dietary Restrictions

Participants who are randomized to the CAB + RPV arm and choose to participate in the oral lead in should take the recommended dosage of oral CAB 30 mg + RPV 25 mg once daily with a meal. Co-administration of antacid supplements has the potential to decrease oral cabotegravir absorption and has not been studied. Antacid products containing polyvalent cations are recommended to be administered at least 2 hours before or 4 hours after oral CAB.

If the participant is randomized to BIK and calcium-containing supplements can be taken together, without regard to food. BIK should be administered at least 2 hours before iron supplements or taken together with food. BIK should be administered at least 2 hours before, or with food 2 hours after antacids containing magnesium and/or aluminium.

5.5.2. Cosmetic Surgery

Participants who are randomised to the BIK or CAB +RPV arm will be questioned at the end of the study if they had any cosmetic surgery during the course of the study only. Cosmetic procedures such as liposuction/liposculpture/implants (but not limited to) may affect metabolic endpoints CCI [redacted] CCI [redacted] Therefore, such patients will be excluded from the final analyses for these

metabolic endpoints. Cosmetic procedures involving the face and neck are out of scope as such procedures are unlikely to have an impact on these metabolic endpoints.

6. STUDY INTERVENTION

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

In this study, investigational product (IP) refers to oral BIK single tablet regimen (or alternately BIK), oral CAB, and CAB LA, which will be supplied by GlaxoSmithKline and oral RPV and RPV LA which will be supplied by Janssen Pharmaceuticals.

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

6.1. Study Intervention(s) Administered

6.1.1. Formulations of CAB + RPV

6.1.1.1. Cabotegravir Tablets (CAB)

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

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. RPV tablets should be stored according to the product labeling.

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

6.1.1.3. Cabotegravir Injectable Suspension (CAB LA)

CAB LA (GSK1265744 LA) is manufactured by GlaxoSmithKline and is a sterile white to slightly pink suspension containing 200 mg/mL of GSK1265744 as free acid for administration by intramuscular (IM) injection. The product is packaged in a glass vial with a 13 mm gray stopper and aluminum seal. Each vial is for single-dose use containing a withdrawable volume of 2.0 mL (400 mg) or 3 mL (600 mg) and does not require dilution prior to administration. CAB LA injectable suspension is to be stored according to the product labeling.

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

6.1.1.4. Rilpivirine Injectable Suspension (RPV LA)

RPV LA (also named JNJ-16150108-AAA), 300 mg/mL Extended Release Suspension for Injection (G001), is provided by Janssen Research & Development, LLC, a division of Janssen Pharmaceuticals, as a sterile white suspension containing 300 mg/mL of RPV as the free base. The route of administration is by intramuscular (IM) injection. RPV LA is packaged in a single use 4 mL glass vial with a 13 mm grey stopper and aluminum seal. Each vial contains a nominal fill of 2.0 mL (600 mg) or 3.0 mL (900 mg) and does not require dilution prior to administration. RPV LA injectable suspension is to be stored according to product labeling. RPV LA should also be protected from light.

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

6.1.2. Biktarvy Tablets (BIK)

BIK is a three-drug fixed dose combination product containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF manufactured by Gilead Sciences. The recommended dosage of BIK is one tablet taken orally once daily with or without food in adults and pediatric patients weighing at least 25 kg. The tablets are purplish brown, capsule-shaped, film-coated, and debossed with “GSI” on one side and “9883” on the other side. Each bottle contains 30 tablets, a silica gel desiccant, polyester coil, and is closed with a child resistant closure. BIK tablets are to be stored according to product labelling.

6.1.3. Medical Devices

- The medical devices to be used in this study are: syringe, vial adaptor and needle.
- Instructions for medical device use are provided in the Study Reference Manual (SRM).

- All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.3.8 and Section 10.9 and appropriately managed by the sponsor.

6.2. Treatment Assignment

Informed consent must be obtained prior to any study procedures, including Screening visit activities. Participants will be assigned to study treatment in accordance with the randomization schedule. The randomization schedule, including stratification, will be generated using the GSK validated randomization software RANDALL NG. The randomization schedule is comprised of a series of blocks, with 2:1 treatment allocation within each block, which are shared across centers via central randomization.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Given the open-label study design, central randomization was used to eliminate selection bias due to foreknowledge of randomized treatment. With central randomization, knowledge at a site of the randomized treatment group for previous participants does not predict which treatment group will be assigned to the next randomized participant.

Randomization and study treatment assignment will be facilitated by the interactive response technology (IRT) through the central Randomization and Medication Ordering System Next Generation (RAMOS NG).

Following confirmation of fulfillment of study entry criteria, study site personnel will be required to register participants using RAMOS NG for assignment of a unique identifier (designating the participant's randomization code and treatment sequence assignment) for each participant participating in the study. On Day 1, A unique treatment number (randomization number) in ascending numerical order will be assigned for each participant participating in the study at each study site. Participants will be randomized in a 2:1 ratio to CAB LA + RPV LA Q2M or to continue BIK in accordance with the computer-generated randomization schedule. Returned study intervention should not be re-dispensed to participants.

Participants who successfully complete 12 months of treatment and have a viral load <50 c/ml at Month 11/12 (or upon retest 4 weeks later) will be given the opportunity to enter the Extension Phase in which they will continue to receive their CAB LA + RPV LA regimen or switch from BIK to CAB LA + RPV LA. In addition, RAMOS NG will facilitate the initial supply and subsequent resupply of IP to study sites.

6.3.2. Blinding

This will be an open-label study and therefore no blinding is required. No summaries of the study data according to actual randomized treatment groups will be available to sponsor staff prior to the planned Month 6 interim analysis. Public presentation of the

Month 6 analysis will not be done prior to the last participant's Month 12 (OLI and BIK)/Month 11 (D2I) visit.

6.4. Dosage and Administration

Participants will be randomly assigned to receive treatment with CAB LA + RPV LA Q2M or BIK taken orally once daily. Participants who choose to participate in the oral lead in will initiate their randomized treatment regimen with Oral CAB 30 mg + RPV 25 mg once daily for 4 weeks, followed by CAB LA + RPV LA IM injections initiating at Month 1. Participants transitioning directly to CAB LA + RPV LA IM injections will initiate their randomized treatment regimen at Day 1. If the participant is randomly assigned to continue the oral standard of care therapy, BIK will continue to be administered as was done prior to the study. Regardless of treatment arm assignment, the investigator should instruct all participants on the importance of treatment adherence. This study has an open-label design. Dosing is outlined in the table below.

Maintenance Phase and Extension Phase (Day 1 to End of Study[+])	
Q2M Arm – Optional Oral Lead In (OLI)	
Oral Lead-In	
	• Receive last dose of BIK regimen during Day 1 visit • Take 1 tablet CAB 30 mg once daily. • Take 1 tablet RPV 25 mg once daily. *Should be taken together once daily at approximately the same time each day, with a meal.*
First Injections (Loading Dose) – Month 1	
Month 1 (two 3mL injections once)	• Receive last dose of oral CAB + RPV regimen during Month 1 visit • Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Maintenance Injections – every 2 months (Q2M) following Month 1	
Month 2 to End of Study[+] (two 3 mL injections every 2 months)	• Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Q2M Arm- No Oral Lead In (D2I)	
First Injections (Loading Doses) – Day 1	
Day 1 (two 3 mL injections once)	• Receive last dose of BIK regimen during Day 1 visit • Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Maintenance Injections – every 2 months (Q2M) following Month 1	
Month 1 to End of Study[+] (two 3 mL injections every 2 months)	• Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Continuing BIK	
Day 1 to Month 13[+]	• Take 1 tablet BIC 50 mg/FTC 200 mg/TAF 25 mg once daily with or without a meal

(1 tablet dosed orally)	
Extension Phase (Month 13 through End of Study)	
BIK Arm (Transition to CAB LA + RPV LA) – Optional OLI	
Oral Lead-in	
Month 13 to Month 14 (2 tablets once daily)	• Take 1 tablet CAB 30 mg once daily. • Take 1 tablet RPV 25 mg once daily. *Should be taken together once daily at approximately the same time each day, with a meal.*
First Injection (Loading Dose) – Month 14 – Optional Oral Lead-in	
Month 14 (two 3 mL injections once)	• Receive last dose of oral CAB + RPV during Month 14 visit • Receive CAB LA 600 mg given as 1 X **3mL** IM injection • Receive RPV LA 900 mg given as 1 X **3mL** IM injection
Maintenance Injections – every 2 months (Q2M) following Month 14	
Month 15 to End of Study+ (two 3 mL injections every 2 months)	• Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection
Direct to Inject Dosing – if Not Using Oral Lead-in	
First Injection (Loading Dose) – Month 13– Optional Oral Lead-in	
Month 13 (two 3 mL injections once)	• Receive last dose of oral BIK during Month 13 visit • Receive CAB LA 600 mg given as 1 X **3mL** IM injection • Receive RPV LA 900 mg given as 1 X **3mL** IM injection
Maintenance Injections – every 2 months (Q2M) following Month 13 – No Oral Lead-in	
Month 14 to End of Study+ (two 3 mL injections every 2 months)	• Receive CAB LA 600 mg given as 1 X **3 mL** IM injection • Receive RPV LA 900 mg given as 1 X **3 mL** IM injection

+Until locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of CAB LA or RPV LA is terminated
Participants will be given an option to continue their randomized Q2M CAB LA + RPV LA regimen, switch from BIK to Q2M CAB LA + RPV LA (or complete trial participation) at Month 12. If the participant decides not to continue participation in the study, any arrangements for off-study ART should be made in advance of the Month 12 visit.
NOTE: Refer to Section 6.6.1 and Section 6.6.2 for Dosing Considerations for CAB LA + RPV LA and BIK, respectively.

6.5. Packaging and Labelling

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

6.6. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

IP accountability will be evaluated using pill counts of unused IP for patients receiving oral treatment (oral CAB, oral RPV, BIK). This assessment will be conducted, when the participant completes oral CAB and RPV lead-in treatment and BIK in the Maintenance Phase, or any withdrawal that occurs during an oral treatment phase.

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

6.6.1. Dosing Considerations for CAB LA + RPV LA

Vials of CAB LA and RPV LA are each supplied as a suspension and need no further dilution or reconstitution. Since RPV LA requires refrigeration, sites should allow the vial to come to approximately room temperature prior to injecting. The vials should be gently inverted a few times to re-suspend sediments and allow bubbles to subside, and then use a syringe to withdraw the required volume of suspension for IM injection.

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

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

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

Should IM maladministration be suspected at any time (e.g., suspected under or overdose or inadvertent IV dosing), the investigator may consider requesting the participant stay onsite for approximately 2-3 hours post dose for safety monitoring and notifying the Medical Monitor. An ECG or any other supportive testing may be obtained at the discretion of the investigator. CCI [redacted] CCI [redacted]

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

6.6.2. Dosing Considerations for BIK

BIK should be taken exactly as instructed by the investigator. It should not be taken with other HIV-1 medicines. BIK should be administered one time each day with or without food. The dose should not be changed, or administration stopped without informing the medical monitor.

6.7. 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. If oral study treatment is dosed at site, 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 and BIK dosed orally once daily will be assessed by counting returned tablets/capsules during the site visits and documented in the source documents and CRF.

A record of the number of CAB, RPV and BIK 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.

6.8. Protocol Permitted Substitutions

6.8.1. Oral Bridging

In exceptional circumstances, to address pre-planned missed CAB LA + RPV LA dosing visits, in consultation with and approval by the medical monitor, Investigators may provide daily oral CAB 30 mg and RPV 25 mg as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA. In certain circumstances (e.g., prior to steady state dosing and following a >8-week oral bridge) repeating the loading doses of CAB IM and RPV IM may be required. Should a participant require "oral bridging", sites must contact the study Medical Monitor for guidance with treatment and dosing strategies prior to a missed CAB LA + RPV LA dose.

Please refer to Appendix 11in Section 10.11 for study management information during the COVID-19 pandemic.

6.9. Interruption of Study Intervention and Visit/Dosing Windows

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

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

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

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

6.9.1. IM Dosing

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

IM dosing is expected to occur during the week in which the participant's projected visit falls (as according to the date of the first injection). The first injections for participants who choose to start injections immediately will occur at Day 1. The first injections for participants electing to participate in the oral lead are administered at Month 1 (can be performed before lab results become available), and the second injections are given at Month 2.

The participant's projected visit is determined by their first injection date and, ideally, is the same date for every injection. For example, if the1st dose (Month 1) is January 15th, then dose 2 (Month 2) will be February 15th, and dose 3 (Month 4) will be April 15th, etc.

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

Dosing for participants randomized to CAB LA + RPV LA is as follows:

All injections should be planned as single injections per drug.

6.9.1.1. IM injections every 2 months (Oral Lead In):

Month 1 – CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

Month 2 - CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

Month 4 and Q2M thereafter - CAB LA 600 mg + RPV LA 900 mg IM, every 2 months until Month 12, each given as 1 X 3 mL IM injection

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

with IM CAB LA + RPV LA at Month 1 can be performed before central lab results are available and safety parameters are reviewed from the Month 1 visit.

The second loading injection will be administered at Month 2 (CAB LA 600 mg + RPV LA 900 mg), with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring every 2 months thereafter. A -7-day dosing window for the second injection is allowed. **Receiving LA dosing from +1 to +7 days is not recommended and the Medical Monitor must be contacted** before the second IM injection is given. Starting at Month 4 and at subsequent visits, a ±7 day dosing window for injections is allowed. If the injection is expected to fall outside of the dosing window, the Medical Monitor must be contacted to discuss individual participant case management.

6.9.1.2. IM injections every 2 months (Q2M) (Direct to injections):

Participants electing not to receive the oral lead in and are receiving CAB LA + RPV LA Q2M will initiate dosing at the Day 1 visit:

Day 1- CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

Month 1 and Q2M thereafter- CAB LA 600 mg + RPV LA 900 mg IM, each given as 1 X 3 mL IM injection

The second injection will be administered at Month 1 (CAB LA 600 mg + RPV LA 900 mg, with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) every 2 months thereafter. A -7-day dosing window for the second injection is allowed. **Receiving LA dosing from +1 to +7 days is not recommended and the Medical Monitor must be contacted** before the second IM injection is given**.** Starting at Month 3 (third injection) and every 2 months thereafter, a ±7-day dosing window for injections is allowed. If the injection is expected to fall outside of the dosing window, the Medical Monitor must be contacted to discuss individual participant case management.

Any request for the visit/dosing to occur outside of the allowed window must be discussed and agreed with the Medical Monitor prior to dosing. In the event of a late dose, a revised dosing schedule for subsequent dosing may be required and will be communicated to the site staff at the time of approval for continued dosing. Temporary switch to oral dosing of CAB and/or RPV may be an option based on individual participant circumstance as described in Section 6.8.1.

See the SPM for scheduling guidance and further information and examples.

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

6.9.2. Oral Dosing

The Month 1 Visit during the Oral Lead-in Phase for participants randomized to CAB + RPV but choosing to participate in the oral lead in is expected to occur 4 weeks (±3 days) after the Day 1 visit. Visits for participants on the BIK arm are expected to occur every 56 days as projected according to the Day 1 visit. There is a ±3-day visit window, from the projected visit date (Maintenance Phase of the study). However, the number of tablets dispensed should be considered when scheduling the next visit.

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

Visits for participants in the Long Term Follow Up are expected to occur as projected according to the last injection. There is no calendar defined visit window in the Long Term Follow Up Phase. In general, four LTFU visits should occur from the last date of LA therapy until week 52 with clinic visits at months 3, 6, 9 and 12, although the timing of the actual visits are flexible, but not the frequency, in LTFU.

6.10. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not ViiV/GSK is providing specific post-study treatment. Participants randomized to CAB LA + RPV LA arm, who have successfully completed 12 months of treatment will continue to have access to both CAB LA and RPV LA in the Extension Phase until study treatment is either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated. Participants randomized to the BIK arm who have successfully completed 12 months of treatment will be given the option of continuing onto the Extension Phase to receive CAB LA + RPV LA. If these participants choose not to continue, they will end participation in the study after Month 12 will be responsible for obtaining post-study treatment.

6.11. Concomitant Therapy

Participants should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential drug:drug interactions between such treatments and the study drugs. The investigator should evaluate any potential drug:drug interactions at every visit, including reviewing the most current version of the investigator brochures, the U.S and/or local prescribing information for RPV and BIK, especially if any new concomitant medications are reported by participants. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name, route, and the dates of administration are to be recorded.

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 6.11.1). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician.

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

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

Hepatitis C infection treatment is allowed throughout the entire study. If HCV treatment occurs during the study, a DHHS approved HCV regimen should be used to limit any drug-drug interactions that may occur. Options for treatment of HCV should be discussed with the Medical Monitor prior to initiation of therapy.

Antacid and H2 Antagonist Use:

While both oral CAB and RPV have dosing requirements with antacid products containing divalent cations, only oral RPV has requirements for dosing with H2 antagonists. Since co-administration of oral CAB and RPV is required in this study, the most restrictive dosing requirements must be taken into consideration.

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

Concurrent administration of multivitamins is acceptable.

Oral RPV administration only:

- Antacid products containing divalent cations (e.g., aluminium, calcium, and magnesium) must be taken at least 2 hours before or at least 4 hours after RPV.
- H2-Receptor antagonists (e.g. cimetidine, famotidine, nizatidine, ranitidine) may cause significant decreases in RPV plasma concentrations. H2-antagonists must be taken at least 12 hours before or at least 4 hours after taking RPV.
- RPV should not be co-administered with proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.

Administration of clarithromycin, erythromycin and telithromycin is not recommended with RPV due to possible increase in plasma concentration of RPV due to CYP3A enzyme inhibition. Where possible, alternatives such as azithromycin should be considered.

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

BIK: BIK and calcium-containing supplements can be taken together, without regard to food.

BIK should be administered at least 2 hours before iron supplements or taken together with food.

BIK should not be taken simultaneously with supplements containing magnesium and/or aluminium due to the expected substantial decrease of BIC exposure.

BIK should be administered at least 2 hours before, or with food 2 hours after antacids containing magnesium and/or aluminium.

Metformin concentrations may be increased by BIK. Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIK and metformin.

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

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

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

6.11.1. Prohibited Medications and Non-Drug Therapies

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

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Section 5.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SPM). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis [James, 2009].
- Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided due to the immunosuppressive effect and potential decreases in RPV plasma

concentrations; however, short treatment courses with oral prednisone/ prednisolone/methylprednisolone (e.g. adjunctive treatment of pneumocystis pneumonia with 21 days of tapering prednisone) are allowed. A single dose of systemic dexamethasone is permitted, but more than a single dose in a treatment course may cause a significant decrease in RPV plasma concentration and is prohibited. Topical, inhaled or intranasal use of glucocorticoids will be allowed.

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

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

Concurrent with CAB and/or RPV

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

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

Concurrent with RPV

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

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

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

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

Concurrent with either CAB LA or RPV LA

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

Concurrent with BIK

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

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifampicin / Rifampin
- Rifabutin
- Rifapentine
- St. John's wort (*Hypericum perforatum*)
- Dofetilide is prohibited as BIC may inhibit renal tubular secretion resulting in increased dofetilide/pilsicainide concentrations and potential for toxicity.

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

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

6.12. 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 or directly approved by the study Medical Monitor. Protocol waivers or

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

In exceptional circumstances, and in consultation with the Medical Monitor, Investigators may provide oral CAB and/or RPV as a short-term "bridging" strategy for participants who have begun CAB LA + RPV LA (see Section 6.8.1 for additional details). Should a participant need "oral bridging", sites must contact the Medical Monitor for guidance on treatment strategies prior to a missed CAB LA + RPV LA dose. Should a participant not notify the site in advance, the Medical Monitor must be contacted for further treatment guidance.

Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Participant Discontinuation/Withdrawal from the Study

Participants permanently discontinuing study treatments prior to the Month 12 visit are considered to be withdrawn from the study treatments. Participants who enter the Extension Phase but permanently discontinue participation in the Extension Phase prior to commercially available CAB LA + RPV LA are considered to be withdrawn from the study treatments but are not considered to be withdrawn from the study because they will enter the follow Follow-up Phase.

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

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

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

An in-clinic withdrawal visit will also be used to assess participants with ongoing AEs, and serious adverse events (SAEs) related & not related to study drug and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant. The withdrawal visit will be distinct from visits conducted during the LTFU Phase.

Following completion of withdrawal assessments, all participants who received one or more injections of CAB LA+ RPV LA will subsequently enter the LTFU Phase initiating with the Month 3 LTFU visit.

Withdrawal decision coincides with a planned clinic visit:

- For any participant who withdraws prematurely from the Maintenance or Extension Phase during a planned in-clinic study visit, withdrawal assessments and procedures are to be performed (according to the SoA (Section 1.3) instead of the assessments for the active planned visit during which the withdrawal decision is made.

Withdrawal decision occurs between planned clinic visits:

- In the event that a decision to withdraw a participant occurs between clinic visits, participants will be instructed to return for an unscheduled withdrawal visit (within 8 weeks of the last Q2M LA injection received or within 4 weeks if participant is randomised to BIK or during the administration of the OLI (oral CAB and oral RPV) if randomized to CAB LA + RPV LA and choosing to perform the OLI) during which withdrawal assessments according to the SoA (Section 1.3) will be completed. For participants who received one or more injections of CAB LA+ RPV LA **withdrawal assessments must occur prior to initiation of the next ART regimen**.

If withdrawal coincides with the active planned Month 13 visit, HIV-1 RNA will only be assessed if the last HIV-RNA measurement from Month 12 was ≥50 copies per mL (i.e. retest for viral load blip). This will ensure that only the Month 12 viral load assessment or required retest will be counted towards the primary and secondary efficacy endpoint windows.

The in-clinic visit will be recorded as an unscheduled withdrawal visit with the following exception. A withdrawal visit and assessments coinciding with the planned Month 13 visit will be recorded as the Month 13 visit such that the participant can be considered a completer, consistent with the definition of study completer in Section 4.5.

Participants may be prematurely discontinued from the study treatment for any of the following reasons:

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

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

- Participants who are not eligible to continue into the Maintenance Phase.
- Participants who are not eligible, or do not wish to continue on to the Extension Phase.
- Virologic withdrawal criteria as specified in Section 7.1.6 are met;
- Participant requires substitution of ART;
- Participant requires substitution or dose reduction of CAB LA or RPV LA (oral bridging supply and potential for a second loading dose may be permissible following discussion with the Medical Monitor).
- Liver toxicity where stopping criteria are met and no compelling alternate cause is identified (see Section 7.1.2);
- Renal toxicity is met and no compelling alternate cause is identified;
- QT interval (QTc) interval >550 msec from three or more tracings separated by at least 5 minutes and considered causally related to IP.
- Grade 4 clinical AE considered causally related to study drug;
- Participant has a Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement and no compelling alternative cause is identified
- Pregnancy (intrauterine), regardless of termination status of pregnancy (for participants on BIK only)Participant withdrew consent

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

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

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

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

a. The site must attempt to contact the participant and re-schedule the missed visit as soon as possible.
b. The site must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
c. In cases where the participant is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and if necessary, a certified letter to the participant’s

last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

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

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

7.1.1. Liver monitoring event – Increased monitoring

A liver monitoring event is an occurrence of predefined liver chemistry changes that triggers increased monitoring of the participant's liver chemistries, but no action is taken with study treatment unless liver chemistry stopping criteria are met.

Liver monitoring event criteria:

- Baseline ALT ⩽1.5x ULN: ALT ⩾5x ULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity.
- Baseline ALT >1.5x ULN: ALT ⩾3x baseline and <5x baseline and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity

Actions:

- Notify the VH medical monitor within 24 hours of learning of the abnormality to discuss participant safety.
- Participant can continue study intervention
- Participant must return every 2 weeks for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution or stabilisation (ALT <5×ULN on 2 consecutive evaluations)
- If at any time participant meets the liver chemistry stopping criteria, proceed as described below

7.1.2. Liver chemistry stopping criteria

Study treatment or Investigational Product must stop immediately when participant meets one of the criteria described in Table below:

Table 3 Liver Chemistry Stopping Criteria - Liver Stopping Event for phase III - IV studies

Liver Chemistry Stopping Criteria - Liver Stopping Event	
If Baseline ALT ≤ 1.5x ULN	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥ 3xULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
If Baseline ALT > 1.5x ULN	
ALT-absolute	ALT ≥ 5x baseline OR > 500 U/L (whichever occurs first)
ALT Increase	ALT ≥ 3x baseline but <5x baseline persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥ 3x baseline OR > 300 U/L (whichever occurs first) **and** bilirubin ≥ 2xULN
Cannot Monitor	ALT ≥ 3x baseline but <5x baseline and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥ 3x baseline and symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.

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) must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required, and the threshold value stated will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

7.1.2.1. Liver Chemistry Stopping Criteria, Participant Management and Follow-Up

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

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

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

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

- Viral hepatitis serology including:
    - Hepatitis A immunoglobulin M (IgM) antibody;
    - Hepatitis B surface antigen (HBsAg) and Hepatitis B Core Antibody (IgM);
    - Hepatitis C RNA;
    - Hepatitis E IgM antibody;
    - Cytomegalovirus IgM antibody;
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Serum acetaminophen test (N-acetyl-para-aminophenol [APAP] adduct test). The site must contact GSK when this test is required. Please refer to the central laboratory manual.

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

7.1.3. General Guidance on Restart

- The definition of restart is not always clear cut in medical practice. Restarts should be limited to cases in which there is clear evidence that the underlying cause of the liver event is not related to study drug.

- For long acting agents, a restart may actually be continuation of therapy rather than a true re-start due to the timeframe between dose administration relative to decision making on allowing a restart.

- If protocol defined stopping criteria for liver chemistry elevations are met (Section 7.1.2), study drug must be stopped. Participants who meet liver chemistry stopping criteria should not be retreated with investigational product unless an exemption has been approved by the VSLC. The guideline for Restart approved by the VSLC, which is maintained as a separate document must be followed.

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

- Ethics Committee or Institutional Review Board approval of drug restart must be obtained, as required.
- The participant must also provide signed informed consent specifically for the IP restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Participants approved by the VSLC for restart of IP must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol. Longer durations of close monitoring may be required for long acting IP.

7.1.3.1. Drug Restart

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

- immunoallergic injury /HLA association with injury
- alcoholic hepatitis

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

7.1.3.1.1. Drug Restart Following Transient Resolving Liver Events Not Related to IP

Approval by the VSLC for drug restart or additional IM administration can be considered where:

- Abnormalities in liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension, acute viral hepatitis, and liver chemistries have significantly improved.
- If definitive non-study drug related diagnosis, restart will be considered once ALT < 3x ULN (for participants with baseline ALT < 1.5x ULN) or < 3x baseline ALT value (for participants with baseline ALT > 1.5x ULN).
- Ethics Committee or Institutional Review Board approval of drug restart must be obtained, as required.
- If restart / redosing of drug is approved by the VSLC in writing, the participant must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.

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

7.1.4. QTc Stopping Criteria

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

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

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

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

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

7.1.5. Virologic Failure

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

7.1.6. Definition of Protocol-Defined Confirmed Virologic Failure

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

Rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥200 c/mL (Day 1 values are not applicable) after prior suppression to <200 c/mL.

7.1.7. Managing Virologic Failure

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

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

7.1.7.1. HIV-1 RNA Blips

HIV-1 RNA "blips" are not usually associated with subsequent virologic failure [DHHS, 2019]. Although the implications of persistent HIV-1 RNA levels between the lower level of detection and <200 c/mL are unclear, the risk of emerging resistance is believed to be relatively low.

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

Participants who have a HIV-1 RNA ≥50 c/mL and <200 c/mL at the key analysis timepoints (Month 6 and 12 [OLI and BIK] and Months 5 and 11 [D2]) must return to the clinic as soon as possible (but no later than 4 weeks after the date of the Months 6 or 12 [OLI and BIK] and Months 5 or 11 [D2I] visits, respectively) for a repeat HIV-1 RNA test such that the result falls within the same analysis window.

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

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

7.1.7.2. Suspected Virologic Failure

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

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

- Confirmatory testing should be scheduled within 2 to 4 weeks following resolution of any intercurrent illness, during which time the participant should receive full dose of all IP.
- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the participant should receive full dose of all IP.

- If therapy is interrupted* due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dose of all IP.
- The participant should have received full dose of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA testing is done.

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

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

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

7.1.7.3. Confirmed Virologic Failure

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

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

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

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

7.2. 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

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

This Section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA, Section 1.3

The following points must be noted:

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

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

- The timing and number of planned study assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

8.1. Efficacy Assessments

8.1.1. Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the SoA (Section 1.3). Methods to be used may include but are not limited to the Abbott RealTime HIV-1 Assay lower limit of detection (LLOD) 40 c/mL. CCI [redacted] CCI

8.1.2. Lymphocyte Subsets, CD4+ and CD8+

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ and CD8+ lymphocyte counts, ratios) according to SoA (Section 1.3) and Laboratory Assessments (Section 8.2.2).

8.1.3. CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the SoA (Section 1.3). HIV-associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection (see Section 10.3). When assessing CDC stage at Screening/Baseline, consider only the latest available CD4 T-cell count, except when the participant had an active Stage 3 event 6 months prior to Screening. Indicators of clinical disease progression are defined as:

CDC Stage 1 at enrolment → Stage 3 event;
CDC Stage 2 at enrolment → Stage 3 event;
CDC Stage 3 at enrolment → New Stage 3 Event;
CDC Stage 1, 2 or 3 at enrolment → Death.

8.2. Safety Assessments

8.2.1. Clinical Evaluations

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

- Monitoring and recording of all AEs and SAEs. Additional information on the Time Period and Frequency of Detecting AEs and SAEs is provided in Section 1.3.
- Physical exams should be conducted as part of normal routine clinical care. Abnormalities noted during any exam must be recorded in the eCRF (e.g., in the current medical conditions or AE logs).
- Height, weight, waist and hip circumference assessments will be measured per the SoA, Section 1.3. Recommended procedures to measure weight, waist and hip circumference can be found in Section 10.10. Appropriate weight related measurements to capture are weight, body fat %, total body water %, muscle mass, and bone mineral mass.

- Vital signs will include systolic and diastolic blood pressure and heart rate collected after resting for about 5 minutes. Temperature will also be collected.
- Past medical history, family history, social history, medication history. Targeted history on cardiovascular risk (smoking history, family and personal history).
- HIV-associated conditions will be recorded.
- Electrocardiogram: A 12-lead ECG will be performed in a semi-supine position after 5 minutes of rest. On Day 1 (Baseline) of the Maintenance Phase, ECGs should be performed in triplicate prior to first dose. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred (and RR if calculated manually), and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each participant for the site. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations. The same QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- Regular monitoring of hematology, blood chemistry, urinalysis and fasting glucose and lipids (parameters to be tested listed below).
- Periodic assessment of glucose, insulin, and bone, cardiovascular, and renal markers;
- Pregnancy testing. A negative urine pregnancy test is required prior to initiation of IP, any dose of CAB LA or RPV LA or as required by the Medical Monitor following a treatment interruption(s). If serum testing is required locally, the results should be available prior to the visit where urine testing is indicated per the SoA (Section 1.3).
- Evaluation and documentation of all concomitant medications and blood products.
- Injection Site Reactions (ISRs) will be assessed clinically during the Maintenance and Extension Phases for the following:

  Pain, tenderness, pruritis, warmth, bruising, discoloration, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts).
- A clinical assessment (using Division of Acquired Immunodeficiency Syndrome [DAIDS] grading scale) should be performed both before and after an injection to identify resolving and new ISRs. All injection site reactions are considered adverse events. The clinical assessment and interpretation of any ISR, will be documented in the ISR AE eCRF.
- Columbia Suicide Severity Rating Scale (eC-SSRS) will be assessed as per the SoA (see Section 1.3 and Suicidal Risk Monitoring Section 8.2.6).

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

8.2.2. Laboratory Assessments

All protocol required laboratory assessments, as defined in the SoA (see Section 1.3), must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol SoA. Laboratory requisition forms must be completed, and samples must be clearly labeled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE Section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

- All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the protocol Time and Events table.

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

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

Labs will be automatically graded by the central lab according to the DAIDS toxicity scales (See Section 10.4 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events").

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

Table 4 includes lab parameters to be assessed as per the SoA (see Section 1.3). In addition to the protocol-specified laboratory assessments the study Medical Monitor, in

collaboration with the site investigator, may request additional central laboratory assessments be performed to support safety profiling and case management of individual study participants.

Table 4 Safety Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[c]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine clearance[b]
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			
Plasma HIV-1 RNA[e]			
CD4+ and CD8+ cell counts [CD4/CD8 ratio][f]			
Peripheral Blood Mononuclear Cells (PBMCs): Day 1, Month 12, Withdrawal only			
Hepatitis B (HBsAg), anti-HBc, anti-HBsAg, and hepatitis C antibody (Screening)[g]			
Syphilis serology + Reflex Rapid Plasma Reagin (RPR) (Screening and Baseline)			
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)			
Pregnancy test for women of childbearing potential[h]			
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate			
Genetics Sample			
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)			
Renal biomarkers including Cystatin-C (blood), Retinol Binding Protein (RBP, blood/urine); and Beta-2-Microglobulin (B2M, blood/urine)[i]			
Bone biomarkers including: Bone-specific alkaline phosphatase, procollagen type 1 N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D[i]			
CCI [redacted]			
HbA1c, Insulin, HOMA-IR			

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

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

g) HBV DNA will only be performed for participants with a positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).
h) Urine pregnancy test/ serum pregnancy test will be performed according to the SoA (Section 1.3).
i) The intention is to utilize these biomarker data for research purposes; the sponsor will not be reporting real-time results of these assessments to the investigator, except for Cystatin C (Day 1 only) and 25 hydroxy-Vitamin D.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.3. Physical Examinations

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

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems. Height and weight will also be measured and recorded as per the SoA in Section 1.3 above.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- The site of IM injection administration should be assessed at every visit for signs of any possible reaction. See Section 8.3.11.6 for additional information.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.4. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate. These will be recorded as per the SoA, in Section 1.3.

8.2.5. Electrocardiograms

A 12-lead ECG will be performed in a semi-supine position. On Day 1, (Baseline), ECGs should be performed in triplicate prior to first dose. At Day 1, Month 1 (OLI) and Month 12 (OLI)/Month 11 (D2I) of the Maintenance Phase, a 2-hour post dose ECG will be performed for participants receiving CAB LA + RPV LA with an allowable window of ± 30 minutes. An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred, and these calculated numbers can be used for reporting purposes. Otherwise, an appropriately qualified ECG reader must interpret the results. The same interpreter should assess all ECGs for each participant. Regardless, each ECG should be reviewed by a qualified ECG reader. The qualified ECG reader will make the non-calculated ECG interpretations. Refer to the SoA for collection timepoints (Section 1.3). Refer to Section 7.1.4 for [QTc] withdrawal criteria and additional [QTc] readings that may be necessary.

8.2.6. Suicidal Ideation and Behaviour Risk Monitoring

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

Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

Assessment of treatment-emergent suicidality will be monitored during this study using the electronic version of the Columbia Suicide-Severity Rating Scale (eC-SSRS). The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Screening visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. The eC-SSRS is to be administered as a patient completed questionnaire specified in the SoA (Section 1.3). The eC-SSRS will be conducted electronically by telephone or by computer/tablet connected to the internet.

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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.2.

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 intervention and/or study (see Section 7).

Please refer to Appendix 11 in Section 10.11 for study management information during the COVID-19 pandemic.

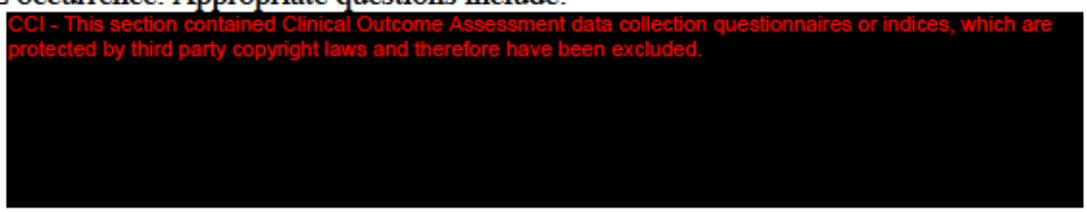
8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- AEs will be collected from the start of Study Treatment until the final follow-up contact, at the timepoints specified in the SoA (Section 1.3).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions Section of the eCRF.
- The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 10.2.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

8.3.2. 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. Appropriate questions include:



8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Section 10.2.

8.3.4. Prompt Reporting of Serious Adverse Events and Other Events

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to the medical monitor once the investigator determines that the event meets the protocol definition for that event. Any seizure or suspected seizure should be reported in an expedited manner, as noted in Table 5.

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

Table 5 Reporting of Serious Adverse Events and Other Events

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

a. Additional details and time frames for reporting supplementary information for cardiovascular and death events are provided in Section 8.3.9.
b. ABC HSR eCRF only required if event meets one of the ICH E2A definitions of seriousness.
c. GSK must be contacted at onset of liver chemistry elevations to discuss participant safety.
d. Liver event documents (i.e., "Liver Event eCRF" and updates, "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

8.3.5. 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.

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.

8.3.6. Pregnancy

8.3.6.1. Pregnancy testing

Women of childbearing potential must have a negative pregnancy test at Screening, and at Baseline (Day 1). Pregnancy testing will also be conducted as per the SoA (Section 1.3) and at any time during the trial when pregnancy is suspected.

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

If pregnancy is confirmed, a discussion with the pregnant study participant assessing the benefit/risk assessment of continuing in the study will be undertaken. If, after this discussion, the participant would like to continue in the study, this will be allowed, provided the pregnant participant signs the pregnancy specific ICF addendum. See Appendix 6 for details. The above is applicable to participants randomised to CAB+RPV and not to participants on BIK.

Pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy.

8.3.6.2. Rationale for Continued Use in Pregnancy

Additional data regarding the use of CAB + RPV LA during pregnancy and management of pregnant participants remaining in the study are found in Appendix 6.

The use of CAB + RPV LA during pregnancy may offer unique benefits. It is well documented that treatment adherence challenges to oral therapy exists both in the peri-partum and post-partum periods with LA dosing offering a unique opportunity to overcome such adherence challenges. LA therapy may also help with nausea (50% mild

to moderate) or hyperemesis (2%) that is frequently see, especially during the first trimester of gestation.

Participants on LA dosing who become pregnant will have exposures throughout pregnancy due to the long half-life and PK tail of CAB/RPV. Prior to this protocol amendment, pregnant participants would have been withdrawn from the study, and initiated on an alternative oral ART regimen. Alternative regimens consist of either 2 or 3 antiretrovirals to protect the life of the mother and for the prevention of MTCT. This regimen, combined with the long half-life and PK tail of CAB/RPV would potentially expose the fetus to additional ARVs during gestation (in some cases upwards of 5 antiretrovirals).

Given the risk/benefit ratio for CAB + RPV LA dosing in WOCBP coupled with concerns of increasing fetal exposure to several additional antiretrovirals upon participant withdrawal, this amendment to the protocol will allow pregnant participants to remain in the study after a pregnancy specific ICF addendum is signed by the participant

8.3.6.3. Time Period for Collecting Pregnancy Information

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

Pregnant study participants who consent to remain in the study during pregnant will continue to have all clinical assessments (with the exception of pregnancy tests) performed as per the Schedule of Activities (Section 1.3), including the collection of additional PK samples for CAB and RPV. See Appendix 6 for details.

Pregnant participants who have received at least one dose of CAB LA or RPV LA and do not continue in the study during pregnancy will enter the Long-Term Follow-Up Phase of the study and will be monitored for 52 weeks after the last dose of CAB + RPV LA. Moreover, an alternative oral HAART will be initiated, at the discretion of the PI and in discussion with the Medical Monitor. If a participant becomes pregnant within 52 weeks of the last dose of study drug, the participant should notify the study site.

8.3.6.4. Action to be Taken if Pregnancy Occurs

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. The investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

Pregnant participants who elect to continue in the study and receive CAB + RPV LA must sign a pregnant specific ICF addendum. Cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CAB + RPV LA; therefore, consideration should be given to the potential for fetal exposure during pregnancy and should be discussed between the study participant and the study PI.

Participants who become pregnant during the study and elect to continue in the study and receive CAB + RPV LA will have additional PK samples collected to monitor CAB LA and RPV LA exposure throughout the pregnancy (see Appendix 6) and at the time of delivery.

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

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

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

Disease related events (DREs) or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 10.3) can be serious/life threatening and will be recorded on the HIV-Associated Conditions eCRF page if they occur. These individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE. If any of the conditions below is met, then record the event on either the AE or SAE page (according to severity) in addition to the HIV Associated Conditions eCRF page. If it is categorized as an SAE, report promptly (i.e., expedited reporting), see Section 8.3.4, to GSK

- The investigator determines that the event or outcome qualifies as an SAE under part 'other situations' of the SAE definition (see Section 10.2.2), or
- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

.

8.3.8. Medical Device Deficiencies

The vial adaptor, syringe, and needles used in the study are classed as medical devices by the FDA. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detecting and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.9.

Instructions for medical device use are provided in the Study Reference Manual.

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator to the manufacturer of the device (if known)

NOTE: The medical devices supplied for the trial will not be supplied or manufactured by GSK/ViiV, reports of medical device deficiencies should be reported to the device manufacturer (if known) through the manufacturers' complaints process.

8.3.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the investigator will notify the manufacturer of the device (if known) within 24 hours.

8.3.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants including those participants who discontinue study intervention or the study and associated persons.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

8.3.8.3. Prompt Reporting of Medical Device Deficiencies to Manufacturer

- Device deficiencies will be reported to the manufacturer of the device (if known) within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.

8.3.8.4. Regulatory Reporting Requirements for Medical Device Deficiencies

The investigator will promptly report all deficiencies occurring with any medical device used for CAB+RPV in the study, to the manufacturer of the device (if known). In order for the manufacturer to fulfil the legal responsibility to notify appropriate regulatory

authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

8.3.9. Cardiovascular and Death Events

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

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

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

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

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

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

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

8.3.10. Toxicity Management

Adverse events that occur during the trial should be evaluated by the Investigator and graded according to the Division of AIDS (DAIDS) toxicity scales (See Section 10.4. “Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events”). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 8.3 and Section 10.2.

8.3.10.1. Treatment Interruption Due to an Adverse Event

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

No toxicity-related dose reductions of IP will be allowed. IP should be restarted as soon as medically appropriate; in general, for oral dosing, this should be no longer than 14 days after discontinuation (unless Grade 3 or 4 toxicities persist). Any interruption in therapy during the Maintenance Phase, oral dosing, of greater than 7 consecutive days must be discussed with and agreed by the Medical Monitor prior to resumption of therapy. The Medical Monitor must be contacted upon becoming aware of resumption in therapy, if therapy was resumed without prior approval (Section 6.9). **IM dosing is expected to occur during the week in which the participant's projected visit falls (as according to the first injection visit). An additional (+ or -) 7-day window, from the projected visit date, is allowable for IM dosing but not preferred.** Any interruption outside of this guidance MUST be discussed with the Medical Monitor prior to reinitiating IM IP (see Section 6.9.1).

Guidance is provided below on general participant management and IP interruptions based on the severity of the AE. Information regarding permitted substitutions \ is provided in Section 6.8. All changes in the IP regimen must be accurately recorded in the participant's eCRF.

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

8.3.10.2. Grade 1 or Grade 2 Toxicity/Adverse Event

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

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

8.3.10.3. Grade 3 Toxicity/Adverse Event

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

- If the Investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by IP, dosing may continue after discussion with the Medical Monitor.
- Participants who develop a Grade 3 AE or toxicity, which the Investigator considers related or possibly related to the IP, should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, IP may be re-started.
- Should the same Grade 3 AE recur within 28 days in the same participant, the IP should be permanently discontinued and the participant withdrawn from study.
- Participants experiencing Grade 3 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and to have withdrawal study evaluations completed. A follow-up visit should be performed 4 weeks after the last dose of IP. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the LTFU Phase for 52 weeks of follow up.
- Participants with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue IP if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 8.3.11.1). Isolated Grade 3 lipid abnormalities do not require withdrawal of IP.

8.3.10.4. Grade 4 Toxicity/Adverse Event

- Participants who develop a Grade 4 AE or toxicity must have IP permanently discontinued. However, if the Investigator has compelling evidence that the AE is not causally related to the IP, dosing may continue after discussion with, and assent from, the Medical Monitor. Participants should be rechecked each week until the AE returns to Grade 2.
- Participants experiencing Grade 4 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above. Any participant receiving at least one dose of CAB LA and /or RPV LA who discontinue IP / Withdraw will initiate treatment with HAART and enter the LTFU Phase for 52 weeks of follow up.
- Participants with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the Medical Monitor, may continue therapy if the Investigator has compelling evidence that the toxicity is not related to IP, with the exception of liver chemistry stopping criteria (See Section 8.3.11.1). An in-clinic follow-up visit will be performed approximately 4 weeks after the last dose of study medication if AEs, SAEs, or laboratory abnormalities considered potentially harmful to the participant are ongoing at the last on-study visit. Isolated Grade 4 lipid abnormalities do not require withdrawal of IP.

8.3.11. Specific Toxicities/Adverse Event Management

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

Participants who permanently discontinue study drug for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-up study evaluations as noted in Section 8.3.3.

8.3.11.1. Liver Chemistry Stopping and Follow-up Criteria

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

8.3.11.2. Seizures

A small number of seizure cases have been reported following CAB administration (less than 1% of all those receiving CAB in clinical studies).

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

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

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

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

8.3.11.3. Decline in Renal Function

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

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

8.3.11.3.1. Proximal Renal Tubule Dysfunctions (PRTD)

PRTD is defined as:

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

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

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

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

8.3.11.4. Proteinuria

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

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

8.3.11.5. QTc Prolongation

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

participant receiving drug known to cause prolonged QT or TdP), then IP may be restarted after consultation with, and agreement by, the Medical Monitor.

8.3.11.6. Injection Site Reactions (ISRs)

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

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

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

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

8.3.11.7. Allergic Reaction

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

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

8.3.11.8. Abacavir Hypersensitivity Reaction (ABC HSR)

If a study participant discontinues study IP, enters into the LTFU period and are administered an ABC-containing product, please follow the information contained within this section.

Background

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR). A detailed clinical description of this reaction (including the type and severity of events that can occur on re-challenge or reintroduction following ABC interruption for non-HSR reasons) and guidance regarding its

management are included in the Local Country Prescribing Information for EPZICOM. Investigators must familiarize themselves with this information on ABC HSR in the Local Country Prescribing Information for each of these products prior to initiating participants on ABC therapy.

Studies have shown that carriage of the *HLA-B*5701* allele is associated with a significantly increased risk of a HSR to ABC. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*5701* and subsequently avoiding ABC in *HLA-B*5701* positive patients, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$). In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of participants who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively.

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

8.3.11.8.1. Essential Patient Information

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

- Participants must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased in individuals who are *HLA-B*5701* positive.

- Participants must also be informed that *HLA-B*5701* negative individuals can also experience abacavir hypersensitivity reaction. Therefore, ANY participant who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT their doctor IMMEDIATELY.

- Participants who are hypersensitive to abacavir should be reminded that they must never take any abacavir containing medicinal products (e.g., ZIAGEN, EPZICOM, KIVEXA, TRIZIVIR, or TRIUMEQ) again, regardless of their *HLA-B*5701* status.

- In order to avoid restarting abacavir, participants who have experienced a hypersensitivity reaction should be asked to return any remaining EPZICOM / KIVEXA tablets to the Investigator or site staff.

- Participants, who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor

before restarting EPZICOM / KIVEXA as more severe symptoms may recur within hours and may include life-threatening hypotension and death.

- Each participant should be reminded to read the Package Leaflet included in the EPZICOM / KIVEXA pack. They should be reminded of the importance of removing the Alert Card included in the pack and keeping it with them at all times.

8.3.11.8.2. Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH E2A), 1994 definitions of seriousness listed in Section 10.2.2 then, in addition to reporting the case as an SAE, the ABC HSR eCRF should also be completed within one week of the onset of the hypersensitivity reaction. Clinically suspected cases of HSR to ABC that do not meet criteria as an SAE can be recorded as an AE.

8.3.11.9. Rash Without ABC HSR Symptoms

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

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

CAB is an analogue of DTG and mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. No instances of serious skin reaction, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme, have been reported for DTG in clinical trials. For further characterization of HSR and rash observed with DTG-containing ART, please see the current version of the IB [GlaxoSmithKline Document Number RPS-CLIN-004375, 2021].

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

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

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

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

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings – see Section 10.4).

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

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

Any rash that is possibly related to study drug, and is present between Day 1 and The Month 1b visit for participants in the Oral Lead-in Phase, must be discussed with the Medical Monitor prior to initiation of CAB LA or RPV LA.

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

8.4. Treatment of Overdose

For participants receiving oral study intervention, any tablet intake exceeding the total daily dose will be considered an overdose.

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

Should IM maladministration, specifically overdose or inadvertent IV dosing, be suspected at any time, the participant will stay onsite for approximately 2-3 hours post

dose for safety monitoring and an ECG will be performed at 2 hours post dose. The Medical Monitor will be notified in the event of a suspected maladministration.

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

For participants randomized to BIK, in the case of an overdose, the participant should go to the nearest hospital emergency room immediately.

For the purposes of this study, an overdose is not an AE (refer to Section 10.2.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a SAE (see Section 10.2.2).

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

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

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

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

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

8.5. Pharmacokinetics

Plasma samples will be collected throughout the Maintenance, Extension and LTFU Phases of the study and stored for potential determination of CAB and RPV concentrations. Samples (blood and plasma) for potential determination of RPV concentrations will be protected from light at all times, from sampling collection through analysis.

8.5.1. Rationale of PK Sampling Strategy

Blood sampling for CAB and RPV concentrations will be performed during the Maintenance Phase of the study for potential evaluation of PK in HIV infected

participants. The PK visits and sampling scheme at each visit detailed in Section 1.3 is based on known PK profiles to support interim and final PK analyses planned in this study.

8.5.2. PK Sample Collection

Blood samples for storage of CAB (2 mL each) and RPV (2 mL each) plasma PK concentrations will be collected from all participants as described in Table 6. Assay results for stored samples may be requested on an ad hoc bases for various reasons including cases of suspected virologic failure or AEs. Although expected to be minimal, any plasma concentrations that are generated will be listed by individual participant number.

For participants transitioning from oral CAB + RPV at Month 1 and Month 14 (BIK to CAB LA+ RPV LA in Extension Phase), PK samples should be collected within the window of 20-28 hours after the last administered oral dose of CAB + RPV was taken the day prior to the clinic visit. Participants will take their final dose of oral CAB + RPV in the clinic after the pre-dose PK sample.

For CAB + RPV participants, on the clinic day where PK is collected, the date and time of dosing administration and the actual date and time of the PK samples, must be recorded on the eCRF.

Pregnant participants will have additional PK samples collected during the duration of the pregnancy. See Appendix 6 for details.

Table 6 CAB and RPV Plasma Pharmacokinetic Sample Schedule

Group	Analytes	PK Sample Times Relative to Dose
Participants receiving CAB LA + RPV LA **Q2M** injections	CAB and RPV	Maintenance Phase Pre-Dose: (OLI participants) Months 1, 2, 4, 6, 8, 10, and 12; (D2I participants) Months 1, 3, 5, 7, 9, and 11 Extension Phase Pre-Dose: (BIK to OLI participants) Month 14, 15; (BIK to D2I) participants Month 14 • A PK sample will be taken at Withdrawal. • PK samples for storage only. • Long-term follow-up Period (off-drug; storage sample): Months 3, 6, 9, and 12.

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

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

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

Samples for determination of RPV will be protected from light throughout handling.

8.5.3. Sample Analysis

8.5.3.1. CAB Sample Analysis

If elected or required, plasma CAB bioanalysis will be performed under the control of IV/IVT BIB, 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). No human DNA analysis will be performed on these samples.

8.5.3.2. RPV Sample Analysis

If elected or required, plasma RPV bioanalysis 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. No human DNA analysis will be performed on these samples.

CCI

[redacted]

8.7. Genetics

See Section 10.7 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SPM.

8.8. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide PBMCs and plasma for storage samples according to the SoA (see Section 1.3) for potential viral genotypic and phenotypic analyses.

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

8.8.1. HIV-1 Polymerase Viral Genotyping and Phenotyping

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

CCI

8.9. Immunogenicity Assessments

Not applicable for this study.

8.10. Medical Resource Utilization and Health Economics

Not applicable for this study.

8.11. Value Evidence and Outcomes

Health outcomes assessments will be conducted according to the SoA (Section 1.3). Assessments are recommended to be administered with a paper instrument at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments.

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

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

- Item 11. How easy or difficult have you been finding your treatment to be recently?

- Item 12. How satisfied are you with the amount of discomfort or pain involved with your present form of treatment?

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

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

CCI

[redacted]

We will conduct (optional) qualitative interviews with SOLAR Investigators/Sub-Investigators and/or site staff to evaluate the reasons for investigators in the trial to use, or not to use, the oral lead-in phase before starting cabotegravir injections. The specific aim of the proposed study is to develop a better understanding from investigators of the factors that have driven and may continue to drive LA ART decisions regarding using OLI versus DTI. These would be conducted under a separate IRB approved consent

(where necessary). Investigators' participation in the interviews would be voluntary and results are anonymous and reported in an aggregated format.

8.11.1. Value Evidence and Outcomes Endpoints (Secondary)

All PROs will be performed at the specified time points as listed in the SoA in Section 1.3.

- The "Preference" questionnaire will assess preference for CAB LA + RPV LA every 2 months compared to an oral BIC single tablet regimen as well as reasons for preference.

- Change from Month 2 in Dimension scores (e.g., "Bother of ISRs", "Leg movement", "Sleep", and "Acceptance of ISRs") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of injection questionnaire (PIN).

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

- Change from Baseline (Day 1) in total "treatment satisfaction" score, and individual item scores of the HIVTSQs.

- Change in treatment satisfaction over time and individual item scores (using the HIVTSQc).

CCI

[redacted]

8.12. Biomarkers

Blood and urine are being collected to perform renal and bone biomarker assessments. In addition to measurements of serum creatinine, estimated GFR, and urinary excretion of albumin, protein, creatinine and phosphate, additional renal biomarkers include:

Renal biomarkers:

- Cystatin C (blood),
- Retinol Binding Protein (RBP, blood/urine)
- Beta-2-Microglobulin (B2M, blood/urine).

Bone biomarkers:

- Bone-specific alkaline phosphatase
- Procollagen type 1 N-propeptide
- Type 1 collagen cross-linked C-telopeptide
- Osteocalcin
- 25 hydroxy-Vitamin D

CCI [redacted]

CCI [redacted]

Insulin, HbA1c, and HOMA-IR

CCI [redacted]

Since the intention is to utilize these biomarkers for research purposes and the clinical significance of these results is uncertain, the Sponsor will not be reporting real time results of these assessments to the investigator except for Cystatin C and 25 hydroxy-vitamin D, Insulin, HbA1c and HOMA-IR as per Table 4.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study is to demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every 2 months compared to a BIK single tablet regimen administered once daily over 12 months in suppressed HIV-1 infected antiretroviral therapy (ART)-experienced participants.

Non-inferiority can be concluded if the upper limit of a two-sided 95% confidence interval for the difference in proportion of participants with HIV-1 RNA $\geq$ 50 c/mL at Month 12 between the two treatment arms (CAB LA + RPV LA – BIK) is less than 4%.

Let p_c, p_b be the proportion of participants with HIV-1 RNA $\geq$ 50 c/mL in the CAB LA+RPV LA and BIK arms respectively, then the primary statistical hypothesis can be written as follows:

H_0: $p_c - p_b \geq 4\%$ vs. H_1: $p_c - p_b < 4\%$

9.2. Sample Size Considerations

9.2.1. Sample Size Determination

Sample size was determined based on desired study power. A total of 654 enrolled participants will be randomized in a 2:1 ratio to receive either CAB LA + RPV LA or BIK treatment. Assuming the true proportion of participants with HIV-RNA ≥ 50 c/mL is 2% for CAB LA+RPV LA injectable regimen and 1% for the BIK arm, a non-inferiority margin of 4% and a 2.5% one-sided significance level, the study will provide approximately 85% power to demonstrate non-inferiority of CAB LA+RPV LA to BIK in term of proportions participants with HIV-1 RNA ≥ 50 c/mL at Month 12 (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL). Details of this calculation along with a couple of another sample size scenarios were provided in Table 7.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Assuming a possible 15% of screen failure, a total of ~770 would need to be recruited to achieve ~654 participants to be enrolled and randomized.

Table 7 Sample Size and Power Scenarios

Assumptions			Sample Size		Power* to reject H_0 at α=2.5%
p_c	p_b	NI Margin	CAB LA+RPV LA	BIK	
2%	1%	4%	390	195	80%
2%	1%	4%	436	218	85%
2%	1%	4%	509	255	90%

* Power was calculated using PASS 2019 Non-inferiority Tests for the Difference Between Two Proportions with Miettinen & Nurminen Likelihood Score Test Statistics.

9.2.2. Sample Size Assumptions

9.2.2.1. Rational for non-inferiority margin

According to the FDA's 2015 guidance document (Human Immunodeficiency Virus-1 Infection: Development of ART Drugs for Treatment, November 2015), the margin for switch trials is driven by the largest clinically tolerable virologic failure rate. Per the FDA document, typical rates of virologic failure seen in switch studies range from 1% to 3% and a margin of 4% for virologic failure rate is considered tolerable [CDER, 2015].

9.2.2.2. Proportion of participants with HIV-1 RNA ≥ 50 c/mL assumptions

It was assumed 1% and 2% for the proportion of participants with HIV-1 RNA ≥ 50 c/mL in BIK and CAB LA + RPV LA respectively. These assumptions were based on the following historical data.

Table 8 Observed Proportion of Participants with HIV-1 RNA ⩾ 50 c/mL

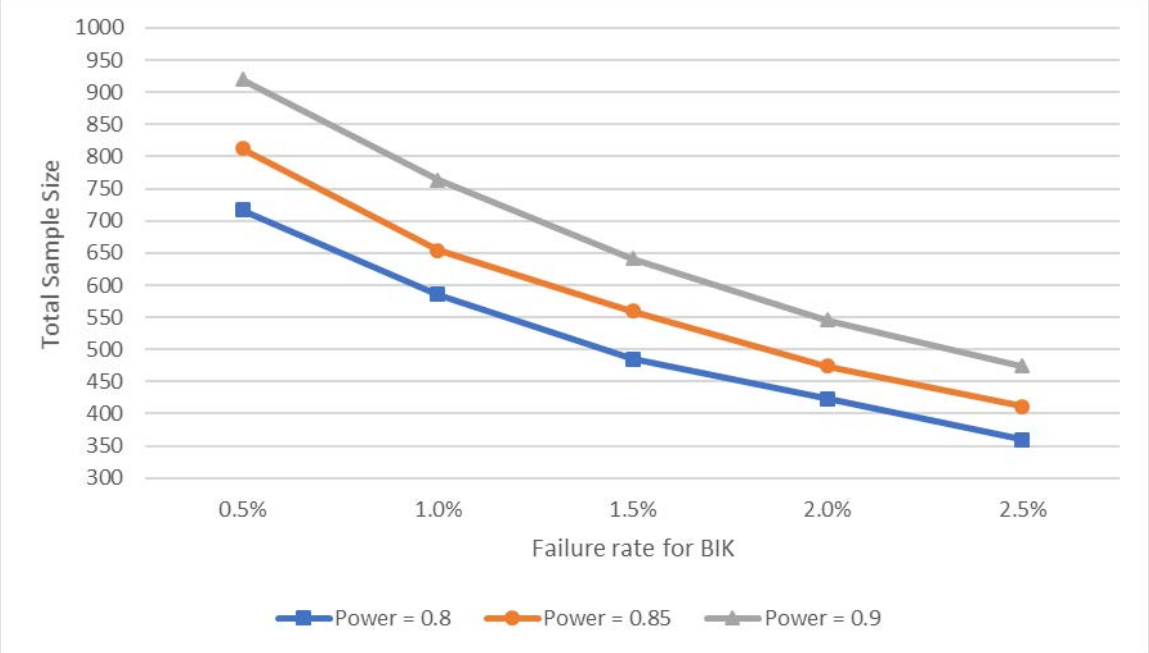
Study	Treatment Arm	Month 12 Proportion of participant with HIV-1 RNA ≥ 50 c/mL
ATLAS-2M[a]	CAB LA+RPV LA	9/522 (1.7%)
GS-US-380-1844[b]	B/FTC/TAF	3/282 (1.1%)
GS-US-380-1878[c]	B/FTC/TAF	5/290 (1.7%)

a. GSK/ViiV Study 207966 Study Week 48 Clinical Study Report [GlaxoSmithKline Document Number 2019N406358_00, 2019]
b. Molina, 2018.
c. Daar, 2018.

9.2.3. Sample Size Sensitivity

Figure 5 shows sensitivity of the required sample size to the true failure rate for the BIK arm assuming 2% failure rate in the CAB LA + RPV LA arm and a 4% non-inferiority margin.

Figure 5 Power and Sample Size Sensitivity to BIK Failure Rate



9.3. Populations for Analyses

The following populations are defined:

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

This population will consist of all randomized participants who receive at least one dose of study medication. Participants will be assessed according to their randomized

treatment, regardless of the treatment they receive. Unless stated otherwise, the ITT-E Population will be used for efficacy analyses.

9.3.2. Per-Protocol Population (PP)

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

9.3.3. Safety Population

The Safety Population will consist of all randomly assigned participants who receive at least one dose of study drug. Participants will be assessed according to actual treatment received. Unless otherwise stated, the Safety Population will be used for safety analyses.

9.3.4. PK Population

The PK Population will include all participants who receive CAB and or RPV and undergo PK sampling during the study and provide evaluable CAB and/or RPV plasma concentration data. Participants in this population will be included in the PK analysis.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database freeze 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.

The study design is open label. However, the central ViiV/GSK team responsible for the conduct and analysis of the study will not review any summaries of data grouped by treatment prior to database freeze for the Month 6 interim analysis.

9.4.1. Primary Analyses

For the primary efficacy analysis, the difference between the two randomized arms for the proportion of participants with HIV-1 RNA ≥50 c/mL at Month 12 (OLI and BIK)/Month 11 (D2I) (according to FDA snapshot algorithm) and its confidence interval will be calculated and be adjusted to the study stratifications using Cochran-Mantel Haenszel (CMH) weights. All CIs will be two-sided. For this analysis, four strata will be formed according to the combinations of levels of the study stratification factors:

- Gender at birth: female
- Gender at birth: male
- BMI: <30 kg/m^2
- BMI: ≥30 kg/m^2

The CMH estimate of the common difference in rates across strata will be calculated as the weighted average of the strata-specific estimates of the difference in response rates between the two arms as follows:

If n_k is the number of CAB LA + RPV LA treated participants, m_k is the number of BIK treated participants, and $N_k = n_k + m_k$ is the total number of participants in the *k*th stratum, then the CMH estimate is given by

$$\hat{d}_{cmh} = \frac{\sum W_k \hat{d}_k}{\sum W_k}$$

where

$$W_k = \frac{n_k m_k}{N_k}$$

are CMH weights and $\hat{d}_k$ are estimates of the differences in response rates between the two treatment arms, p_c-p_b, for the *k*th stratum. The corresponding two-sided 95% CI will be calculated as:

$$\hat{d}_{cmh} \pm 1.96 \times \sqrt{\hat{\text{var}}(\hat{d}_{cmh})}$$

using the variance estimator $\hat{\text{var}}(\hat{d}_{cmh})$, given by [Sato, 1989], which is consistent in both sparse data and large strata. The full equation for this variance estimate will be provided in the statistical analysis plan.

Female participants randomized to CAB + RPV LA who become pregnant while in the study are allowed to continue. Female participants randomized to BIK will not be allowed to continue. For the FDA snapshot algorithm-related efficacy analysis at key time points (Month 5/6 and Month 11/12), viral load data after confirmed pregnancy may be "censored", to minimize bias between the treatment and the comparator arm. Further sensitivity analysis may be performed as necessary. Data handling details will be provided in the Reporting Analysis Plan.

9.4.2. Safety and Secondary Analyses

The proportion of participants with plasma HIV-1 RNA <50 c/mL using the Snapshot algorithm is a key outcome at Months 6 and 12 (OLI and BIK)/Months 5 and 11 (D2I) and will be judged against a pre-specified non-inferiority margin of -12%.

Changes from baseline in CD4+ lymphocyte count and in CD4+/CD8+ lymphocyte counts ratio and resistance data will be summarized. The incidence of HIV-1 disease progression (AIDS and death) will be presented.

The proportion of participants with plasma HIV-1 RNA <50 c/mL using the Snapshot algorithm and changes from baseline in CD4+ lymphocyte count will be summarized by subgroups (e.g., age, gender and race)

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

Exposure to study medication, measured by the number of weeks on study drug, will be summarized by treatment group. The proportion of participants reporting AEs will be tabulated for each treatment group. The following summaries of AEs will be provided:

- Incidence and severity of all AEs
- Incidence and severity of treatment related AEs
- Incidence and severity of AEs leading to withdrawal
- Incidence of SAEs

CCI [redacted]

Laboratory and vital signs data will be summarized by visit and treatment group. In addition, the number and percentage of participants with graded laboratory toxicities (based on DAIDS categories) will be summarized by treatment group. The proportion of participants experiencing changes from Baseline in their National Cholesterol Education Program (NCEP) lipid categories will be summarized by treatment arm. Further details of safety analyses will be included in the RAP.

9.4.3. Health Outcome Analyses

The Preference, PIN, HIVTSQs and HIVTSQc, CCI [redacted] CCI [redacted] will be summarized as detailed in Section 8.11. Details of the analyses to be performed will be specified in the RAP.

9.4.4. Viral Genotyping/Phenotyping Analyses

The incidence of observed genotypic and phenotypic resistance to study ART will be summarized by treatment arm for participants meeting confirmed virologic withdrawal criteria. Details of the analyses to be performed will be specified in the RAP.

9.4.5. Pharmacokinetic Analysis

Plasma CAB and RPV concentration data will be listed and summarized by week, day and planned sampling time in both tabular and graphical forms. PK parameters will be summarized as well if available.

9.5. Interim Analyses

The main analysis will be conducted to evaluate the primary objective of the protocol when all participants have completed their Month 12 (OLI and BIK)/Month 11 (D2I) visit. An interim analysis will be conducted when all participants have completed their Month 6 (OLI and BIK)/Month 5 (D2I) visit. To minimise bias, the Month 6 interim results will not be shared with any participant and with most investigators. However, when a lead author(s) for a potential abstract presentation of the Month 6 interim results

is (are) identified, that investigator(s) and the other co-authors on the abstract will have access to the interim results prior to its presentation. No other investigators will have knowledge of this data prior to the last participant completing their last visit for the primary Month 12 analysis. A Month 6 interim analysis abstract may be submitted to a conference for consideration only if the conference convenes after the Month 12 data collection has been completed.

The interim analyses will include analyses on the primary and secondary efficacy endpoints, as well as key safety endpoints. Full details of the interim analyses will be specified in the Reporting and Analysis Plan (RAP).

Further data cuts and analyses may be conducted as necessary to support regulatory submissions, publications or for other purposes. Additionally, information collected on pregnant participants as collected in the eCRF may be reported descriptively or listed on an interim basis (see Appendix 6 for further details). No adjustment for multiplicity caused by repeated analysis on the primary endpoint will be made as the interim analysis will be secondary. Type I error rate will not be inflated for the treatment comparison at the final analysis as non-inferiority will not be assessed at the interim.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. 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.

10.1.3. Informed Consent Process

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

Participants who are rescreened are required to sign a new ICFGSK (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 or about the study disease; 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.

The ICF may contain a separate section that addresses the use of participant data and remaining samples for optional further research. Where approved by the IRB/IEC, the investigator or authorised designee will inform each participant of the possibility of further research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate tick box may be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research. Participants who decline further research will tick the corresponding "No" box.

10.1.4. 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

10.1.5. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.1.6. Dissemination of Clinical Study Data

- Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of participants begins.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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.

10.1.7. 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.
- Guidance on completion of the CRF will be provided in
- Quality tolerance limits (QTLs) will be pre-defined in the (location) to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- 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 and contracts.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the

currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. 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 and contract.

10.1.9. 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.

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If 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

10.1.10. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.1.11. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

- Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of participants begins.

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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

Events <u>NOT</u> 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.

10.2.2. 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 <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

10.2.3. Definition of Cardiovascular Events

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

10.2.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (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.
- Participant-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-up of AE and SAE

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

10.2.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

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

10.3. Appendix 3: CDC Classification for HIV-1 Infection (2014)

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

HIV infection, stage 0

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

HIV infection, stage 1

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

HIV infection, stage 2

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

HIV infection, stage 3 (AIDS)

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

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

HIV infection, stage unknown

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

Stage-3-defining opportunistic illnesses in HIV infection

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

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

Reference

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

10.4. Appendix 4: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017

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

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

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

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

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

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

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

Endocrine and Metabolic

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

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

Endocrine and Metabolic

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

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

Gastrointestinal

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

Gastrointestinal

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

Musculoskeletal

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

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

Neurologic

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

Neurologic

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

Pregnancy, Puerperium, and Perinatal

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

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

Psychiatric

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

Respiratory

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

Sensory

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

Systemic

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

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

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

Systemic

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

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

Urinary

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

Site Reactions to Injections and Infusions

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

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

*Laboratory Values**
Chemistries

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

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

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

Chemistries

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

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

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

Chemistries

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

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

Chemistries

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

Hematology

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

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

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

Hematology

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

Urinalysis

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

Reference

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

10.5. Appendix 5: Contraceptive Guidance

10.5.1. 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.

10.5.2. Contraception Guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 9

Table 9 Highly Effective Contraceptive Methods

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

NOTES:

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

10.6. Appendix 6: Information and Guidance for Managing Pregnant Participants

10.6.1. Collection of Pregnancy Information:

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in the protocol in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Females who become pregnant while in the study may remain in study, and continue scheduled dosing with CAB + RPV LA, once a pregnancy ICF addendum is signed by the participant.
- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed as per the study Time and Events Table. Pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing will be performed and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided.

10.6.2. Introduction

Pregnancy increases the risk of HIV progression, while HIV increases the risk for maternal complications from pregnancy and poses the risk of perinatal HIV transmission

to the unborn fetus. Mother to child transmission (MTCT) of HIV can occur during pregnancy, labor, delivery or postpartum through breastfeeding. In the absence of any interventions, vertical HIV transmission rates approximate 35%, but fall below 5% with effective interventions [WHO, 2010]. In the United States and other developed countries, the risk of perinatal infection has decreased from 25% without intervention to less than 2% with intervention [WHO, 2012]. The HIV-infected mother who breastfeeds her infant while taking ARVs herself or giving ARVs to her infant reduces the risk of transmission to about 2% after 6 months of breastfeeding, or 4% over 12 months [UNAIDS, 2011].

The 2013 WHO Guidelines thus recommend (strong recommendation, moderate-quality evidence) all pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART [WHO, 2013]. The global benefits anticipated from ART in pregnant women who are eligible for treatment include treatment of the mother's underlying HIV disease, eliminating pediatric transmission/infection and reducing sexual transmission of HIV

Recent recommendation updates to treatment guidelines have included objectives to increase HIV screening of patients, including pregnant women (noting the importance of adopting HIV screening to be a part of prenatal care).

The ART recommendation for pregnant females prioritizes the health of women over potential risks and increased cost. For females who are on ARV therapy at the time that they become pregnant, the WHO recommends that they continue such therapy if they are responding to the ARV.

In line with this recommendation, this study will allow those females participating in 213500 who are receiving CAB + RPV LA but become pregnant on study, to continue in the study in order to maintain their effective regimen with minimal disruption. The PK of CAB + RPV LA, characterization of the safety of CAB + RPV LA administered during pregnancy, and characterization of maternal, birth and infant outcomes following treatment with CAB + RPV LA will be examined.

10.6.3. Background

At the time of finalizing this protocol, there have been 25 pregnancies reported during the CAB/RPV LA P3 development program (including 6 during PK tail and 5 during OLI) with 8 pregnancies leading to live births (including 3 pregnancies exposed during the PK tail of treatment and 1 pregnancy exposure occurring during CAB oral lead-in) and 5 on-going pregnancies.

- A total of 12 pregnancy losses (11 of these occurring during the first trimester)
- Missed abortions: 2 (one of these was a twin anembryonic pregnancy)
- Elective abortions (no medical indication): 5
- Elective abortion for nausea and vomiting: 1

- Spontaneous abortions: 4 (1 late spontaneous abortion at 23/40; severe Intrauterine growth restriction [IUGR], placental insufficiency; presence of risk factors)

No reported congenital anomalies

10.6.4. Benefit/Risk Assessment

Discuss with the pregnant participant the benefit-risk of continuing in the study and continuing to receive CAB + RPV LA injections, or being withdrawn from study, as a result of her pregnancy. All participants who chose to stay in the study during pregnancy, and who choose to continue to receive CAB + RPV LA injections will need to sign a pregnancy specific ICF addendum.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CAB + RPV LA (CABENUVA) during pregnancy. Healthcare providers are encouraged to register all pregnant study participants, whether or not they choose to remain in the study, by calling the Antiretroviral Pregnancy Registry] at 1-800-258-4263.

10.6.4.1. Cabotegravir

Cabotegravir use in pregnant females has not been evaluated and there are insufficient human data on the use of during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage.

The rate of miscarriage is not reported in the APR. The background risk for major birth defects and miscarriage for the indicated population is unknown. The background rate for major birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) is 2.7%. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation.

Animal Data (pre-clinical)

Cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1000 mg/kg/day from 15 days before cohabitation, during cohabitation, and from Gestation Days 0 to 17. There were no effects on fetal viability when fetuses were delivered by caesarean although a minor decrease in fetal body weight was observed at 1000 mg/kg/day (greater than 30 times the exposure in humans at the RHD). No drug-related fetal toxicities were observed at 5 mg/kg/day (approximately 13 times the exposure in humans at the RHD) and no drug-related fetal malformations were observed at any dose.

Cabotegravir was administered orally to pregnant rabbits at 0, 30, 500, or 2000 mg/kg/day from Gestation Days 7 to 19. No drug-related fetal toxicities were observed at 2000 mg/kg/day (approximately 0.7 times the exposure in humans at the RHD).

In a rat pre- and postnatal development study, cabotegravir was administered orally to pregnant rats at 0, 0.5, 5, or 1000 mg/kg/day from Gestation Day 6 to Lactation Day 21. A delay in the onset of parturition and increases in the number of stillbirths and neonatal deaths by Lactation Day 4 were observed at 1000 mg/kg/day (greater than 30 times the exposure in humans at the RHD); there were no alterations to growth and development of surviving offspring. In a cross-fostering study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to cabotegravir-treated mothers were nursed from birth by control mothers. There was no effect on neonatal survival of control pups nursed from birth by cabotegravir-treated mothers. A lower dose of 5 mg/kg/day (13 times the exposure at the RHD) was not associated with delayed parturition or neonatal mortality in rats. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in fetal tissue.

During the pre-clinical development of CAB, there were no positive genotox findings. Embryo-fetal studies also showed no adverse findings including neural tube defects. In a pre and postnatal study, there were some test article-related decreases in F1 pup survival (87.4% vs 98.9% in control) in the highest dose (1000 mg/kg/day) during postnatal days 1-4. No findings in the 0, 0.5 and 5 mg/kg/day doses).

The clinical significance of these finding in humans is unknown.

Human Data

Cabotegravir use in pregnant females has not been evaluated and there are insufficient human data on the use of CAB + RPV LA during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage.

While there are insufficient human data to assess the risk of NTDs with exposure to CAB + RPV LA during pregnancy, NTDs were associated with dolutegravir, another integrase inhibitor. A preliminary analysis of an ongoing birth outcome surveillance study in Botswana involving women exposed to DTG, a different molecule in the same integrase class of medications as CAB, identified 4 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 2824 women. More recently, data from the Tsepamo study was updated. In April 2020, the Tsepamo study team provided interim data from the study, which included available data through to 29 February 2020. Subsequently, the study team presented an updated analysis, including data through to 30 April 2020, at the 23rd International AIDS Society (IAS) Meeting [Zash, 2020].

The latest data from the Tsepamo study included additional data accrued between 1 April 2019 (the cut-off for the last formal analysis) and 30 April 2020. Over this 13-month period, 39,200 additional births were recorded, including 1908 additional exposures to DTG at conception. Two additional NTDs were detected in 1908 (0.10%) deliveries to mothers taking DTG at conception, compared with 6 NTDs in 4569 (0.13%) deliveries in mothers taking non-DTG regimens at conception, of which 5 NTDs in 2999 (0.17%) deliveries were to mothers taking efavirenz at conception. The incidence in HIV negative mothers over the 13-month period was 17/30,258 (0.06%).

A causal relationship of these events to the use of DTG has not been established.

The incidence of NTDs in the general population ranges from 0.5-1 case per 1000 live births. There are insufficient human data on the use of CAB + RPV LA during pregnancy to adequately assess a drug-associated risk of miscarriage or birth defects, including NTDs.

10.6.4.2. Rilpivirine

Animal Data

Rilpivirine was administered orally to pregnant rats (40, 120, or 400 mg/kg/day) and rabbits (5, 10, or 20 mg/kg/day) through organogenesis (on Gestation Days 6 through 17, and 6 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with rilpivirine in rats and rabbits at exposures 15 (rats) and 70 (rabbits) times the exposure in humans at the RHD. In a pre- and postnatal development study, rilpivirine was administered orally up to 400 mg/kg/day through lactation. No adverse effects were noted in the offspring at maternal exposures up to 63 times the exposure in humans at the RHD

Human Data

Based on prospective reports to the APR of over 390 exposures to oral rilpivirine-containing regimens during the first trimester of pregnancy and over 170 during second/third trimester of pregnancy, the prevalence of birth defects in live births was 1.3% (95% CI: 0.4% to 3.0%) and 1.1% (95% CI: 0.1% to 4.0%) following first and second/third trimester exposures.

Available data from the APR show no difference in the overall risk of birth defects for rilpivirine compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the MACDP

In a clinical trial, total oral rilpivirine exposures were generally lower during pregnancy compared with the postpartum period. Refer to Edurant Prescribing Information for additional information on rilpivirine.

10.6.5. Clinical Considerations

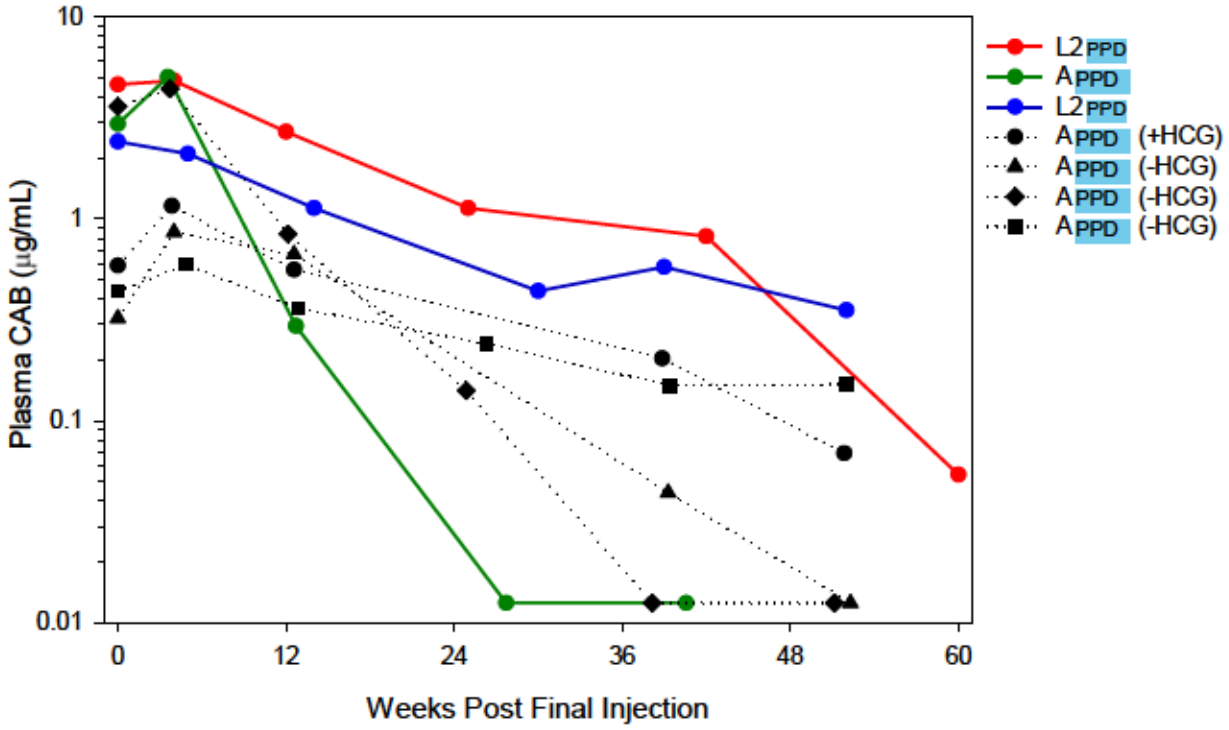
10.6.5.1. Exposure

Lower exposures with oral rilpivirine were observed during pregnancy. Cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CAB + RPV LA; therefore, consideration should be given to the potential for fetal exposure during pregnancy.

With the change in volume of distribution associated with pregnancy, drug concentrations of CAB and RPV during pregnancy will be assessed in pregnant participants who contiune to receive LA therapy while on study. For these participants, plasma PK samples of CAB and RPV will be obtained at every study visit for Q8W and Q4W during the pregnancy. Additionally, all other scheduled assessments, including viral load

monitoring, will continue as reflected in as described in the protocol in the SOA (see Section 1.3)

Figure 6 LTFU PK in Female and Pregnant Participants (LATTE-2, ATLAS)



10.6.5.2. Use of Supplements with CAB + RPV LA

During pregnancy, additional supplements including vitamins, minerals and other mediations including over the counter (OTC) medications may be prescribed to the pregnant woman. It is important for all female participants who remain in the study to be aware of any potential drug drug interactions (DDIs) that may occur with study medications and other agents used during pregnancy.

10.6.5.2.1. Oral Cabotegravir Only

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

Concurrent administration of multivitamins is acceptable.

10.6.5.3. Overall Benefit: Risk Conclusion

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Additional considerations when using CAB + RPV LA can be found in the protocol in Section 2.3.3

There is limited data regarding the use of CAB + RPV LA in pregnant females. Based on animal data, the use of CAB + RPV LA is not anticipated to increase the risk of adverse developmental or reproductive outcomes in humans. Available data from the APR show no difference in the overall risk of birth defects for rilpivirine compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the MACDP.

Refer to Section 10.6.4.1 and Section 10.6.4.2 for additional data.

The use of CAB + RPV LA during pregnancy may offer unique benefits. It is well documented that treatment adherence challenges to oral therapy exists both in the peri-partum and post-partum periods with LA dosing offering an opportunity to overcome such adherence challenges. LA therapy may also help with nausea (50 % mild to moderate) or hyperemesis (2%). Female participants on LA dosing who become pregnant will have exposures throughout pregnancy due to the long half-life and PK tail of CAB/RPV. Pregnant participants who are withdrawn from study and are initiated on an alternative oral ART regimen consisting of either 2 or 3 antiretrovirals to protect the life of the mother and for the prevention of MTCT, potentially expose the fetus to additional ARVs during gestation (in some cases upwards of 5 antiretrovirals).

In summary, taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with CAB + RPV LA are justified by the anticipated benefits that may be afforded to pregnant participants with HIV infection.

Given the risk/benefit ratio for CAB + RPV LA dosing in WOCBP, coupled with concerns of increasing fetal exposure to several additional antiretrovirals upon participant withdrawal, pregnant participants will be allowed to remain in the study and continue to

receive CAB + RPV LA injections, once the new pregnancy ICF addendum is signed by the participant.

10.6.6. Study Assessments and Procedures: specific assessments for pregnant participants

Participants who become pregnant while in the study, and who sign the informed consent pregnancy addendum may remain in the study and continue to receive CAB + RPV LA.

Please note: The HIV care provider is responsible for HIV care and will collaborate and share information with the participant's obstetric care provider, discuss the participant's participation in this study, the necessary procedures at delivery, to share HIV information, and to collect birth and infant outcomes from the participant's obstetric care provider and/or the pediatric health provider for the infant.

Because obstetric and/or pediatric care will not be specifically provided via this study, the participant must also establish appropriate obstetric and pediatric care (including prenatal care) per local standard of care (SOC) in parallel. It will be necessary for the participant to provide a release of medical information to facilitate collection of pregnancy and pregnancy outcomes by the investigator

All assessments will be conducted in accordance with the protocol, as described in the protocol in the SoA (see Section 1.3)

10.6.6.1. Plasma HIV-1 RNA

Women who become pregnant while on study and consent to stay on study will have viral load (VL) testing obtained at every study visit during pregnancy and at the first post-partum visit.

10.6.6.2. Safety Assessments

Pregnancy related complications and diagnoses, and outcomes will be captured as AEs and SAEs as outlined in the protocol in Section 8.3.2.

Pregnancy complications (e.g., preeclampsia or eclampsia, prolonged hospitalization after delivery, for wound infections etc, seizures) and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

In the event of a pregnancy loss, after the loss is confirmed the participant may continue to receive CAB + RPV LA unless they meet the criteria for confirmed virologic withdrawal. They may continue to CAB + RPV LA until study medications are locally approved and commercially available or until they no longer receive benefit. In this case the participant must agree to use contraception to avoid a 'new' pregnancy (See Appendix 6).

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

10.6.6.3. Pharmacokinetics

All pregnant participants who elect to remain in the study will have additional PK pre-dose sampling obtained at each study visit. Each PK blood draw for pregnancy PK will comprise of the following:

- CAB PK - 2mL (protein bound analysis)
- CAB PK - 9 mL (protein un-bound analysis)
- RPV PK - 2mL

CCI [redacted]

A final PK sample for cabotegravir and rilpivirine concentrations will obtained at the first postpartum LA visit. All PK samples will be collected prior to the scheduled LA injection. The pre-dose PK sample is to be collected within 15 minutes prior to the LA dose, on the day of the study visit.

Please refer to the SPM for PK sample collection, processing, and shipping instructions. The actual date and time of each PK sample collection will be recorded in the eCRF.

Data collected on CRF from pregnant participants will be reported as detailed in a separate section of the analysis plan or separate analysis plan and additionally may be pooled with other studies.

10.7. Appendix 7: Genetics

Genetic Research Objectives and Analyses

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

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

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

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

Study Population

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

Study Assessments and Procedures

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

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

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to

the participant by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

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

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

Informed Consent

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

Participant Withdrawal from Study

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

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

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

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

- If a participant withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

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

and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

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

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

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

10.8. Appendix 8: Liver Safety: Required Actions, Follow-up Assessments and Study Intervention Guidelines

10.8.1. VSLC Guidelines for Drug Restart after stop for Liver criteria

Drug Restart refers to resuming study treatment following liver events meeting stopping criteria **in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis)**. Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury. (Table 10; Figure 7).

DRUG RESTART

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

- immunoallergic injury /HLA association with injury
- alcoholic hepatitis

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

10.8.2. VSLC Decision Process for Drug Restart Approval or Disapproval

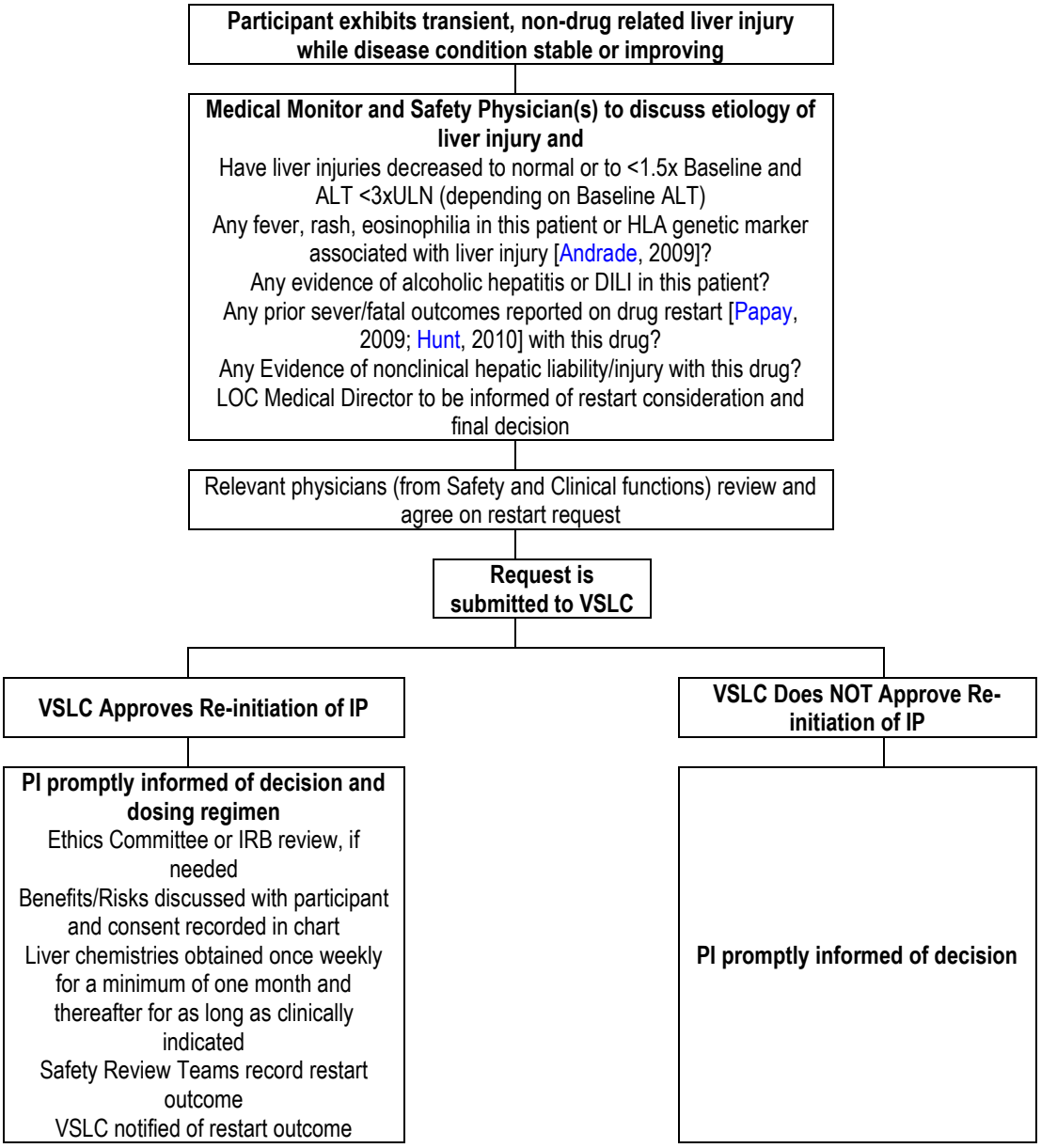
- Principal Investigator (PI) requests consideration of drug re-initiation for a participant stable or improving on IP, who exhibits liver chemistry elevation meeting participant stopping criteria, which is transient, non-drug-related, and liver chemistries have improved to normal or are within 1.5x Baseline and ALT< 3xULN depending on baseline ALT as per Section 7.1.3.1.1.
- GSK Medical Monitor and GCSP Physician to review the participant's diagnosis restart risk factors (Hepatotoxicity Panel consultation is available) and complete checklist (Table 10).
  - ***must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history***.
- The local operating company (LOC) medical director should be informed that study drug restart is under consideration and of the final decision, whether or not to proceed.
- Relevant physicians (listed below) must review and agree on action to be taken regarding request for drug restart:
- Safety ReviewTeam Leader, Safety Development Leader, or Senior Safety Physician
- MDL and PPL

- Request is taken to VSLC for final decision

Table 10 Checklist for Phase III drug restart after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, congestive heart failure (CHF), acute viral hepatitis), and improvement of liver chemistry to normal or ≤1.5x baseline & ALT<3xULN

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

Figure 7 VSLC process for drug restart approval or disapproval



10.8.3. Medical monitor, GCSP Physician and PI actions for Restart following VSLC decision

10.8.3.1. Medical Monitor and GCSP Physician Actions

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

reported to Line Management including, VSLC Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

10.8.3.2. PI Actions:

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

Drug Restart Outcomes Table Template

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

Drug Restart Outcomes Table – Update with each event

Protocol#	Participant#	Restart?	Safety outcome*	Drug benefit

Restart safety outcomes:

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

10.9. Appendix 9: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.3 for the list of GSK medical devices).

10.9.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. 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 an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.9.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event **that:**
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: o A life-threatening illness or injury. 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. o A permanent impairment of a body structure or a body function. o Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. o Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function o Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product

Serious adverse device effect (SADE) definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated serious adverse device effect (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

10.9.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.9.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK and ViiV in lieu of completion of the GSK/AE/SAE/device deficiency form. • There may be instances when copies of medical records for certain cases are requested by GSK or ViiV. 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.

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
  - Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
  - Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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) or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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/SAE/device deficiency

- 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/SAE/device deficiency 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 form.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.9.5. Reporting of SADEs

SADE Reporting to GSK

- NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- Any device deficiency that is associated with an SAE must be reported to the manufacturer of the device (if known) within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

10.10. Appendix 10: Recommendation for Assessment of Waist Circumference, Hip Circumference and Weight (Adapted from WHO STEPS Surveillance Manual, 2017) and for Resting Blood Pressure

10.10.1. Waist Circumference

Equipment

To take waist circumference measurements you will need a:

- Constant tension tape (for example, Figure Finder or Myo Tape Body Tape Measure);
    - Tape measures will be provided for the study
- Chair or coat stand for participants to place their clothes.

Privacy

A private area is necessary for this measurement. This could be a separate room, or an area that has been screened off from other people.

Preparing the participant

This measurement should be taken without clothing, meaning, directly over the skin.

If this is not possible, the measurement may be taken over light clothing (for example, a hospital gown, an undergarment or thin t-shirt). Thick or bulky clothing must be removed. Body shaping garments are not allowed to be worn during this measurement.

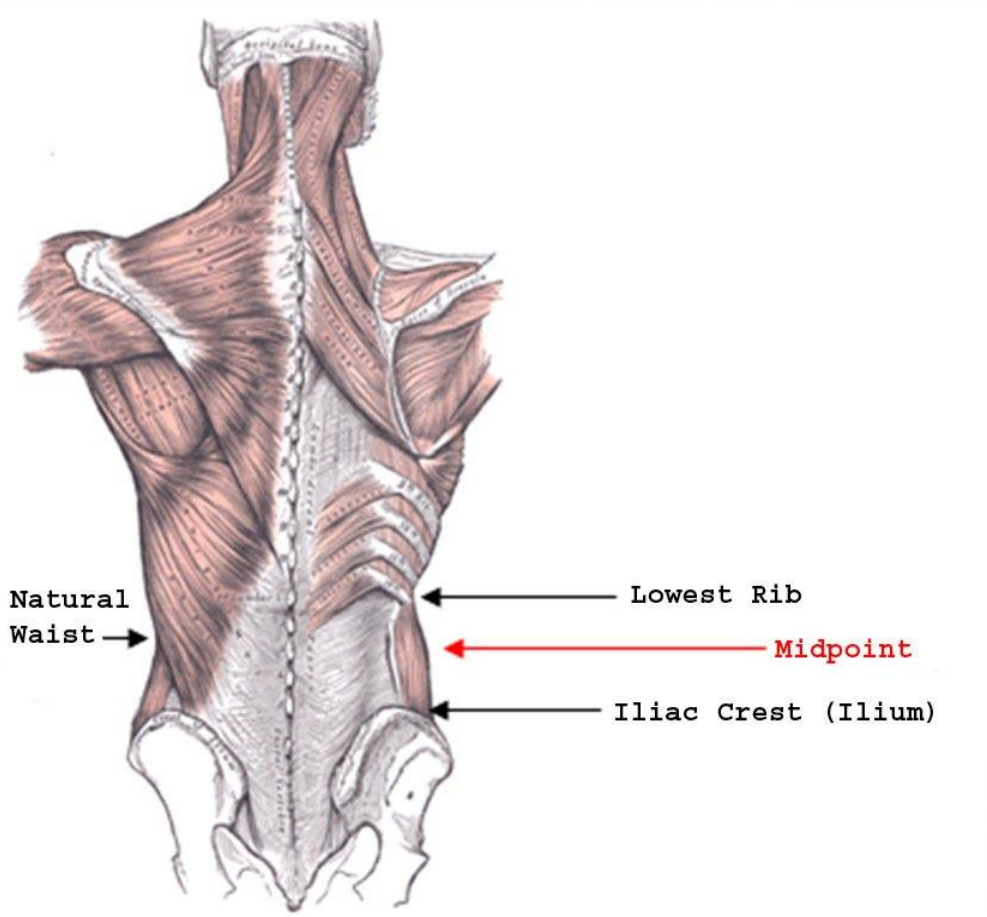
How to take the measurement

We recommend having the same study staff performing the measurement across visits for individual study participants.

This measurement should be taken:

- at the end of a normal expiration;
- with the arms relaxed at the sides;
- at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (hip bone) (Figure 8).

Figure 8 Location of Midpoint for Waist Circumference Measurement



Procedure

Follow the steps below to measure the waist circumference of a participant:

1. Standing to the side of the participant, locate the last palpable rib and the top of the hip bone. You may ask the participant to assist you in locating these points on their body.
2. Wrap the tension tape around the participant and position the tape at the midpoint of the last palpable rib and the top of the hip bone, making sure to wrap the tape over the same spot on the opposite side.

Note: Check that the tape is horizontal across the back and front of the participant and as parallel with the floor as possible.

3. Ask the participant to:
   - stand with their feet together with weight evenly distributed across both feet;
   - hold the arms in a relaxed position at the sides;
   - breathe normally for a few breaths, then make a normal expiration.

4. Measure waist circumference and read the measurement at the level of the tape to the nearest 0.1 cm, making sure to keep the measuring tape snug but not tight enough to cause compression of the skin.
5. Record the measurement, in **centimetres to one decimal place**, within the eCRF.

- ***Note: Measure once and record.***

10.10.2. Hip Circumference

Equipment

To take hip circumference measurements you will need a:

- Constant tension tape (for example, Figure Finder or Myo Tape Body Tape Measure);
    - Tape measures will be provided for the study
- Chair or coat stand for participants to place their clothes.

Privacy

A private area is necessary for this measurement. This could be a separate room, or an area that has been screened off from other people. Hip measurements are taken immediately after waist circumferences.

Preparing the participant

This measurement should be taken without clothing, that is, directly over the skin.

If this is not possible, the measurement may be taken over light clothing (for example, a hospital gown or an undergarment). Thick or bulky clothing must be removed. Body shaping garments are not allowed to be worn during this measurement.

How to take the measurement

We recommend having the same study staff performing the measurement across visits for individual study participants.

This measurement should be taken:

- with the arms relaxed at the sides
- at the maximum circumference over the buttocks.

Procedure

Follow the steps below to take hip circumference measurements.

1. Stand to the side of the participant and wrap the tension tape around them.
2. Position the measuring tape around the maximum circumference of the buttocks.

3. Ask the participant to:
    - Stand with their feet together with weight evenly distributed over both feet;
    - Hold their arms relaxed at the sides.
4. Check that the tape position is horizontal all around the body and snug without constricting.
5. Measure hip circumference and read the measurement at the level of the tape to the nearest 0.1 cm.
6. Record the measurement, in **centimetres to one decimal place**, within the eCRF.

Note: Measure once and record.

10.10.3. Weight

Equipment

To measure weight, you will need a weighing scale, (such as a Tanita BC-587 or Tanita BC-730 scale). Alternatively, a BMI scale measuring both height and weight (e. g. Growth Management Scale) can be used.

Ensure the scale has been regularly calibrated according to the manufacturer instructions and that calibration documentations are filed and available to the study CRA as required.

We recommend using the same scale across visits for individual study participants.

We recommend having the same study staff performing the measurement across visits for individual study participants.

We recommend that the time of day a participant's weight is measured is consistent for every participant at the site within the study. (ex. If measured at 10 a.m. at initial measurement, attempt to have the participant measured at 10 a.m. at subsequent visits).

Set up requirements

Make sure the scales are placed on a firm, flat surface. Do not place the scales on:

- carpet
- a sloping surface
- a rough, uneven surface.

Set up scales

Follow the steps below before measuring the weight of a participant:

1. Make sure the scale is on a firm, flat surface.
2. Turn on the scale and wait until the display shows 0.0.

Procedures

Follow the steps below to measure the weight of a participant:

1. Ask the participant to remove their footwear (shoes, slippers, sandals, etc). They should also take off any heavy belts and remove all objects out of their pockets (example: mobile phones, wallets, coins).
2. Ask the participant to step onto scale with one foot on each side of the scale.
3. Ask the participant to:
    - stand still
    - face forward
    - place arms on the side and
    - wait until asked to step off.

Record the weight in **kilograms to one decimal place** in the eCRF.

References

[WHO STEPS Surveillance Manual, 2017; 3-5-9 to 3-5-13.]

10.10.4. Resting Blood Pressure

General instructions

- Ensure that healthcare professionals taking blood pressure measurements have adequate initial training and periodic review of their performance.
- Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained and regularly recalibrated according to manufacturers' instructions.
- When measuring blood pressure in the clinic or in the study site, standardise the environment and provide a relaxed, temperate setting, with the person quiet and seated, and their arm outstretched and supported. Use an appropriate cuff size for the person's arm.
- Measure the blood pressure in one arm (in semi-supine* position or seated after 5 minutes rest).

*Semi-supine position: Laying /sitting back (at 45° angle or variations) in a relaxed position with feet touching a flat surface.

10.11. Appendix 11: COVID-19 Pandemic and Clinical Trial Continuity

Background

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

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

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

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

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

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

10.11.1. Changes to Study Visits and Study Procedures

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

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

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

10.11.2. Changes to Informed Consent

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

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

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

10.11.3. Permissible Use of Antiretroviral Therapy

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

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

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

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

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

Oral bridging with CAB + RPV

The protocol permits oral bridging to cover planned missed injections with oral CAB + RPV, only until IM dosing can be resumed. The start date of oral bridging should be within the dosing window for the missed IM dosing visit. This recommendation can be used to accommodate requests for oral dosing due to COVID-19. Oral bridging recommendations should be followed as per protocol Section 6.8.1. The process and required information for requesting oral bridging can be found in your Study Reference/Procedure Manual. Please continue to reach out to your study medical monitor for approval of oral bridging, in order to document use and to ensure expeditious shipment of oral CAB + RPV to your site.

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

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

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

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

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

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

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

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

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

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

10.11.5. COVID-19 Experimental Agents

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

10.11.6. COVID-19 Specific Data Capture

10.11.6.1. Capturing COVID-19 Specific Protocol Deviations

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

10.11.6.2. Capturing COVID-19 Specific AEs and SAEs

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

Please use the following guidance:

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

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

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

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

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

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

Suspected case:

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

OR

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

OR

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

Probable case:

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

OR

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

Confirmed case:

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

Covid-19 Contact:

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

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

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

10.12. Appendix 12: Country-specific requirements

10.12.1. United Kingdom (UK)

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

Study Duration: In this study, the Extension Phase is intended to provide access to CAB LA + RPV LA until CAB LA + RPV LA receives local (by country) regulatory approval and becomes commercially available. Therefore, the duration of the Extension Phase may vary from country to country and is dependent on the recruitment time for the study and the time taken to achieve local approval for marketing. For participants in the UK, estimating a 4- month recruitment period, and with treatment anticipated to be commercially available by approximately 4Q 2021, the Extension Phase is anticipated to conclude around the same time. During this time, participants will be monitored on Q2M to ensure they continue to derive clinical benefit from CAB LA + RPV LA.

Based on the request from Medicines and Healthcare Products Regulatory Agency (MHRA) in United Kingdom, to adjust the Exclusion Criteria Number 11 regarding the participants with a risk of seizures excluded or not in this study and the responsibility of the Investigator making the decision.

Exclusion Criteria # 11:

11. Participants determined by the Investigator to have a high risk of seizures, including participants who had a seizure within the last year without a clear aetiology, or had seizures within the last 12 months while receiving anti-seizure medications will be excluded. Participants with a distant history of seizure without recent seizure activities, or any participant with a history of a controlled seizure disorder while on treatment who has been seizure free and off the anti-seizure medications for >12 months may be enrolled if the Investigator believes the risk of seizure recurrence is low. Other participants with a prior seizure history may be discussed with the Medical Monitor prior to participant's enrolment

10.12.2. Ireland

This requirement has been included as a recommendation by the Health Product Regulatory Authority (HPRA) in Ireland.

Section 10.11.1 (Changes to Study Visits and Study Procedures) states the following: "There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, in order to protect a study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations".

In Ireland this can be submitted as an urgent safety measure or amendment as appropriate as described at the following link: http://www.hpra.ie/homepage/medicines/regulatory-information/clinical-trials/covid-19-(coronavirus)-and-cts/guidance-on-the-management-of-clinical-trials-during-covid-19/.

10.12.3. France (FRA)

This requirement has been included based on requests from the Agence nationale de sécurité du médicament et des produits de santé (ANSM) to adjust the Inclusion and Exclusion criteria regarding the INI and NNRTI resistance mutations excluded in this study in accordance to the EU review process of the Marketing Authorisation Application.

Exclusion Criteria #27

27. Known or suspected presence of any major INI or NNRTI resistance mutations, except for K103N as defined by the IAS-USA resistance guidelines [IAS-USA, 2019] by any historical resistance test result.

    Note: Prior genotypic resistance testing (genotyping of plasma vRNA and/or PBMC vDNA) is not required but if available it must be provided to ViiV, after screening and before randomization according to guidance in the SPM, to provide direct evidence of no pre-existing exclusionary resistance mutations. You must wait for the study virologists to confirm the lack of exclusionary resistance mutations, which will be provided before the screening window closes. Details regarding baseline or prior resistance data must be noted in the source documentation

10.12.4. Germany (DEU)

Based on the request from the German Lead Ethics Committee: to remove study intervention rechallenge.

Based on the request from the German Competent Authority, the Federal Institute for Drugs and Medical Devices (BfArM): to amend Exclusion Criteria 31

Exclusion Criteria 31:

31. Alanine aminotransferase (ALT) ≥ 5x the upper limit of normal (ULN) or ALT ≥3x ULN and bilirubin ≥1.5 x ULN (with > 35% direct bilirubin)

10.13. Appendix 13: Protocol Amendment History

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

Amendment 02, 8-SEP-2021

Overall Rationale for Amendment 2:

The primary reason for protocol amendment 02 is to address and clarify comments raised during the course of the study and to implement country specific changes following regulatory review

Section # and Name	Description of Change	Brief Rationale
Headers	Change of protocol reference number	Due to sponsor protocol writing procedure changes
Section 1.1 and Section 3 - Objectives and Endpoints	Minor rephrase of first secondary objective	
Section 1.3 SoA	Clarification to SoA (and footnotes): -addition of ISR Assessment for IM injection at Month 13 in BIK to Direct to Inject Extension phase -removal of CV assessments at months 1 through 6 - BIK to Oral Lead In – Extension Phase table: 12 Lead ECG, removed “triplicated at Day 1 pre-dose -clarification to footnote “e” footnote “n”: addition of biomarkers in line with protocol body -footnote “u”: clarification for pregnant participants -addition of footnote “gg” – History of cosmetic procedures during the study	For clarification purposes
Section 2 - Introduction	Removal of phrase stating	CABENUVA now approved in

Section # and Name	Description of Change	Brief Rationale
	there are currently no approved two-drug regimen	selected regions
Section 2.1.2 – Weight Gain	Addition of metabolic syndrome classification	To clarify which participants meets metabolic syndrome
Section 2.3.1 Risk Assessment	• Dolutegravir data/Rationale for Risk updated. • Rilpivirine LA update	Updated safety information
Section 3 – Objectives and Endpoints	Replace "…activity…" with "…response with the use …" in secondary objective	For clarification purposes
Section 4.1.2 – Maintenance Phase (Direct to Inject [no oral lead-in])	Define window for second injection	To clarify dosing windows for first and second injections
Section 4.1.3.2 – Participants Entering from the BIK arm	Define window for second injection	For clarification purposes
Section 4.1.4 LTFU Phase – IM Regimen Only	New text added	For clarification purposes
Section 4.2 – Type and Number of Participants	Inclusion of approximately 20% females	Adjust the target based on real world evidence.
Section 4.5 End of Study Definitions	Updated terminology	For clarification purposes
Section 5.1 - Inclusion Criteria	Inclusion Criteria 5 - Clarification that no other ART class other than INI regimen are allowed	For clarification purposes
Section 5.2 – Exclusion Criteria	Exclusion Criteria 2 – specify documented viral load is required	For clarification purposes
Section 5.5.2- Cosmetic	Addition of new section	To inform participants who had

Section # and Name	Description of Change	Brief Rationale
Surgery		cosmetic surgery during the course of the study what happens to their data during analyses.
Section 6.1.3 – Medical Devices	Addition of Medical Devices Section	Regulatory request with CABENUVA approval in selected countries
Section 6.4 – Dosage and Administration	Addition of text in table and footnote.	
Section 6.9.1. – IM Dosing	Rephrasing of visit windows	For clarification purposes.
Section 6.11.1 - Prohibited Medications and Non-Drug Therapies	Addition of Rifampicin to Rifampin in "concurrent with BIK" sub-section	In line with "concurrent with CAB and/or RPV" sub-section
Section 7.1 – Participant Discontinuation/withdrawal from the Study	Addition of reference to BIK in second bullet Rephrasing pregnancy text for BIK participants	For clarification purposes
Section 7.1.3. General Guidance on Restart	Removal of rechallenge text.	Rechallenge option removed.
Section 7.1.7.1 HIV-1 RNA Blips	Specify key analysis timepoints	For clarification purposes
Section 8.2.1 – Clinical Evaluations	Rephrase to "An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals is preferred (and RR if calculated manually),"	To align with electronic Data Capturing From
Section 8.2.5 – Electrocardiograms	Deletion of 2 hour post-dose ECG in BIK arm	For clarification purposes and alignment to SoA
Section 8.3.6 - Pregnancy	Added text throughout all sections to allow participants who become pregnant (on CAB+RPV) to remain in the study:	To allow participants who become pregnant to remain in the study.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.8 – Medical Device Deficiencies	Added new sections detailing the medical device deficiencies reporting requirements.	Added medical device deficiency reporting requirements.
Section 8.5.2 PK Sample Collection	Addition of: Pregnant participants will have additional PK samples collected during the duration of the pregnancy. See Appendix 6 for details.	To allow participants who become pregnant to remain in the study.
Section 8.11 - Value Evidence and Outcomes Endpoints	Changes to last paragraph	To allow optional qualitative surveys for Investigators
Section 8.12 - Biomarkers	Added Insulin, HbA1c and HOMA-IR to last paragraph	To align with Table 4 (Safety Laboratory Assessments) footnotes
Section 9.4.1 – Primary Analysis	Addition of paragraph at end of section	Describing statistical considerations for pregnant participants on CAB+RPV LA
Section 9.5 – Interim Analysis	Rephrasing of first and last paragraph	For clarification purposes
Section 10.1.3 – Informed Consent Process	Changes to last paragraph	For clarification purposes
Section 10.5.2 Contraceptive Guidance	Deleted Footnote B of Table 8	Change to One highly effective contraceptive method should be utilized for 30 days prior to first dose of study medication and for at least 52 weeks after D/C of CAB LA and RPV LA
Section 10.6 – Appendix 6	Addition of new Appendix “Information and Guidance for Managing Pregnant Participants”	To allow participants who become pregnant to remain in the study (on CAB+RPV only).
Section 10.8 – Appendix 8	Removal of Rechallenge	

Section # and Name	Description of Change	Brief Rationale
	guidelines.	
Section 10.8 - Appendix 9	Addition of new Appendix 9 “AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies”	Regulatory request with CABENUVA approval in selected countries
Section 10.12.2 -Ireland	Addition of Ireland Country Specific Request	In reply to Health Product Regulatory Authority (HPRA)
Section 10.13 – Appendix 13: Protocol Amendment History	Addition of changes from Global Protocol Amendment 1 and rationale Local Protocol Amendments 01 in France, GBR and Germany	

Amendment 01, 30-JUN-2020

Overall Rationale for Amendment 1:

The primary reason for protocol amendment 01 is to add minor clarifications to address study completion, PK collection, and endpoint timings. Country-specific details were added to Appendix 10 to address UK MHRA requirements. The protocol short title was updated. Corrections to typographical errors in protocol text and title were made throughout.

Section # and Name	Description of Change	Brief Rationale
Short Protocol Title	Adjusted to more representative for the study on title page and synopsis	To conform to guidelines set forth in the eTrack User Guide
Section 1.3: SoA footnote 'u' and 'g'	PK sample acquisition clarified in footnote Added specific weight related measurements to collect in eCRF	To remove any confusion of how many PK samples to acquire for participants who receive OLI at start of Maintenance and Extension. Also, important for specific weight related measurements to be captured to ensure reason to collect in eCRF is supported.
Section 3: Objectives and Endpoints and throughout the protocol as applicable	Clarification of when participants reach endpoints	To provide clarity that only one sample per product is required.
Section 4.5; End of Study definition	Update of completion scenarios to be inclusive of Month 13	Section 7.1 and Section 4.5 were contradictory and needed to be aligned.
Section 6.3.2; Blinding	Added language regarding blinding and when data will be viewed by ViiV/GSK staff	To conform to analysis plan for study
Section 8.2.1; Clinical Evaluations	Added language that points site staff to SRM for appropriate measures to capture regarding weight gain	To provide clarity on location of measures to collect

Section # and Name	Description of Change	Brief Rationale
Section 8.2.5; ECG/Section 1.3 SoA footnote 'i'	Added clarity to when ECGs were performed based on randomized arm	To provide clarity on ECG procedures
Section 8.5.2	Removal of requirement of Pre-dose samples for LTFU visits	Participant is off drug and a PK sample can be taken at any time during LTFU visit
Section 9.1; Statistical Hypotheses	Updated language to terminology used in this study (Q8W to Q2M; Week 48 to Month 12)	To keep terminology the same throughout document.
Section 9.4; Statistical Analysis	Added language regarding blinding and when data will be viewed by ViiV/GSK staff	To conform to analysis plan for study
Section 10.10; Country specific requirements	Added UK country-specific details	UK has specific details necessary to meet regulatory requirements
Section 10.11; Protocol Amendment History	Added appendix to protocol	Added per protocol template requirements
Throughout protocol	Minor typographical and grammar errors addressed	Since minor, no need to list individually.

Amendment 01 / France 01, 16-NOV-2020

Overall Rationale for Country-Specific Amendment:

Based on requests from the:

- Agence nationale de sécurité du médicament et des produits de santé (ANSM) in France, to adjust the Exclusion criteria number 27 regarding the major INI and NNRTI resistance mutations excluded in this study.
- French Ethics committee, to adjust the introduction as few biotherapies are proposed to simplify patients treatment.

Section # and Name	Description of Change	Brief Rationale
Section 2 Introduction	Removal of while the phrase "there are no currently approved two-drug regimens to maintain suppression, simplifying treatment has long been a goal to increase treatment compliance and improve the quality of life for patients with HIV" from the second paragraph	This request was required for France
Section 5.2 Exclusion Criteria	Adjustments to include major INI and NNRTI resistance mutations	This amendment was required for France

Amendment 1/GBR-1: 20-NOV-2020

Overall Rationale for Country-Specific Amendment:

Based on the request from Medicines and Healthcare Products Regulatory Agency (MHRA) in United Kingdom, to adjust the Exclusion Criteria Number 11 regarding the participants with a risk of seizures excluded or not in this study and the responsibility of the Investigator making the decision.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion	Adjustments to clearly define the exclusion criteria and clarify the responsibility of the Investigator to	This amendment was required for United Kingdom

Section # and Name	Description of Change	Brief Rationale
Criteria	make the decision regarding enrolment eligibility	
Section 10.10 Appendix 10: Country-specific requirements	Additions to specify the UK requirement on Exclusion Criteria Number 11	This amendment was required for United Kingdom

Amendment 01 / DEU01, 12-JAN-2021

Overall Rationale for Country-Specific Amendment: Based on the request from the German Lead Ethics Committee: to remove study intervention rechallenge.

Based on the request from the German Competent Authority, the Federal Institute for Drugs and Medical Devices (BfArM): to amend Exclusion Criteria 31

Section # and Name	Description of Change	Brief Rationale
Section 5.2	Expand Exclusion Criteria 31 parameters	BfArM requirement
Section 7.1.3 Restart Section 10.7 Appendix 7: Liver Safety: Required Actions, Follow-up Assessments and Study Intervention Restart Guidelines	Deleted study intervention rechallenge after stopping treatment for liver criteria	Ethics Committee requirement

10.14. Appendix 14: Abbreviations and Trademarks

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
ADE	Adverse device effect
ADL	Activities of Daily Living
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core Antibody
Anti-HbsAg	Antibodies against Hepatitis B surface Antigen
APAP	N-acetyl-para-aminophenol
APR	Antiretroviral Pregnancy Registry
ARV	Antiretroviral
ART	Antiretroviral therapy
ATLAS 2M	**A**ntiretroviral **T**herapy as **L**ong **A**cting **S**uppression every **2** **M**onths
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-τ)	Area under the concentration curve from 0 hours to the time of next dosing
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAB	Cabotegravir
CAB LA	Cabotegravir long-acting
c/mL	Copies/milliliter
cART	Combination antiretroviral therapy
CCR5	C-C chemokine receptor type 5
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CDC	Centers for Disease Control and Prevention
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
CMH	Cochran-Mantel Haenszel
ConART	Concomitant Antiretroviral Therapy
CSR	Clinical Study Report
C-SSRS	Columbia Suicidality Severity Rating Scale
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
CSR	Clinical Study Report
CV	Cardiovascular
CVF	Confirmed Virologic Failure

COVID-19	Coronavirus Disease 2019
DDI	Drug Drug Interaction
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DRE	Disease-Related Events
DRV	Darunavir
DTG	Dolutegravir, TIVICAY
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eC-SSRS	Columbia Suicide Severity Rating Scale
eCRF	Electronic case report form
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ETR	Etravirine
EU	European Union
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FTC	Emtricitabine
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
HbsAg	Hepatitis B surface Antigen
HAT-QoL	HIV/AIDS-targeted quality of life
HBV	Hepatitis B virus
HCG	human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HIV TSQ	HIV treatment satisfaction questionnaire
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
IAS	International AIDS Society
IB	Investigator’s Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IM	Intramuscular
INI	Integrase inhibitor
INR	International normalized ratio
INSTI	Integrase strand transfer inhibitor

IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IUGR	Intrauterine growth restriction
IRT	Interactive response technology
ISR	Injection Site Reaction
LA	Long Acting
LDL	Low density lipoprotein
LPV	Lopinavir
LPV/r	Lopinavir-ritonavir
LTFU	Long-Term Follow-Up
MACDP	Metropolitan Atlanta Congenital Defext Program
MCV	Mean corpuscular volume
MDR	Medical Device Regulation
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram
MRHD	Maximum recommended oral human dose
MSD=F	Missing, switch, or discontinuation equals failure
MTCT	Mother to child transmission
NTD	Neural tube defect
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRS	Numeric Rating Scale
NRTI	Nucleoside reverse transcriptase inhibitor
OLI	Optional Oral Lead In
OTC	Over the counter
PI	Protease inhibitor
PIN	Perception of Injection
PK	Pharmacokinetic
PP	Per-protocol
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSRAE	Possible suicidality-related adverse event
QTc	Corrected QT interval
Q8W	Every 8 weeks
Q4W	Every 4 weeks
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RBP	Retinol Binding Protein
RHD	Recommended human dose
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RPV	Rilpivirine, Edurant
RPV LA	Rilpivirine long-acting

RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SADE	Serious adverse device effect
SJS	Stevens-Johnson syndrome
SOC	Standard of Care
SPM	Study Procedures Manual
SRM	Study Reference Manual
STR	Single tablet regimen
SVW	Suspected Virologic Withdrawal
TDF	Tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
TMC278	Tibotec Medicinal Compound 278
TSQ	Treatment Satisfaction Questionnaire
ULN	Upper limit of normal
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VAPI	Vaccines' Perception of Injection
VAS	Visual Analog Scale
VL	Viral load
VSLC	ViiV Safety and Labelling Committee
WBC	White blood cell
WOCBP	Women of childbearing potential

Trademark Information

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM/KIVEXA
TRIUMEQ
TRIZIVIR
ZIAGEN

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

11. REFERENCES

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. *Expert Opin Drug Saf*. 2009; 8:709-714.

Antiretroviral Therapy Cohort Collaboration (ART-CC). Durability of first ART regimen and risk factors for modification, interruption or death in HIV-positive patients starting ART in Europe and North America 2002-2009. *AIDS* 2013; 27:803-813.

Antiretroviral Pregnancy Registry (APR) Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2013. Wilmington, NC: Registry Coordinating Center; 2013. Available from URL: www.APRegistry.com.

Arribas J, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklingoff C. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load <50 copies/ml at baseline. *HIV MED,* 2012: Aug;13(7):398-405.

Arribas J, Girard P, Landman R, Rich J, Mallolas J, Martinez-Rebollar M, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor. *Lancet Infect Dis.,* 2015; 15:785-92.

Bierman WF, van Aqtamael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS,* 2009; 23(3):279-91.

Biktarvy Prescribing Information, August 2019.

Bourgi K, Jenkins C, Rebeiro PF, Lake JE, Moore RD, Mathews W.C, et al. Greater weight gain among treatment-naïve persons starting integrase inhibitors. Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 670, 2019.

CDER: Center for Drug Evaluation and Research. Human Immunodeficiency Virus-1 infection: developing antiretroviral drugs for treatment – guidance for industry. US DHHS FDA. November 2015.

Centers for Disease Control and Prevention (CDC) Revised surveillance case definition for HIV infection-United States, 2014. *MMWR Recomm Rep* 2014;63 (RR-03):1-10.

Chevat C, Viala-Danten M, Dias-Barbosa C, Nguyen VH. 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.

Daar ES, DeJesus E, Ruane P, Crofoot G, Oguchi G, Creticos C, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with

HIV-1: 48 week results of a randomized, open-label, multicenter, phase 3, non-inferiority trial. *Lancet HIV*. 2018. 5:e347-56.

Debroy P, Sim M, Erlandson KM, Falutz J, Prado CM, Brown TT, et al. Progressive increases in fat mass occur in adults living with HIV on antiretroviral therapy, but patterns differ by sex and anatomic depot. *J Antimicrob Chemother*. 2019 Apr; 74(4): 1028–1034.

Department of Health and Human Services (DHHS). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Updated December 18, 2019. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed 20 Jan 2020.

Edurant Prescribing Information, May 2021

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced Liver Injury. *J Hepatol* 2019 Jun 70 (6), 1222-1261.

GlaxoSmithKline Document Number 2013N168152_09: A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 For the Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects, LATTE-2. Effective date: November 2017

GlaxoSmithKline Document Number 2017N326521_02: A Phase IIIb, Randomized, Multicenter, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Administered Every 8 Weeks or Every 4 Weeks in HIV-1-infected Adults who are Virologically Suppressed, ATLAS 2M. Effective date: July 2018

GlaxoSmithKline Document Number 2018N380094_00: A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 for The Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects. Week 160 - Clinical Study Report. Effective date: March 2019.

GlaxoSmithKline Document Number 2019N406358_00: A Phase IIIb, Randomized, Multicenter, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Administered Every 8 Weeks or Every 4 Weeks in HIV-1-infected Adults who are Virologically Suppressed, Week 48 CSR. Effective date: December 19, 2019

GlaxoSmithKline Document Number 2019N421460_00. Population pharmacokinetic evaluation of cabotegravir Q8W regimen. Effective date: 09-Dec-2019

GlaxoSmithKline Document Number RPS-CLIN-004375: Clinical Investigator's Brochure for Cabotegravir Annual IB Update Version 11. Effective date: February 2021.

Grundy SM, Hansen B, Smith SC, Cleeman JI, Kahn RA. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association Conference on scientific issues related to management. Circulation. 2004 Feb;109:551-556

Hill A, McCann KM, Pilkington V, Moorhouse MA, Sokhela S, Serenata CM, et al. Risk of metabolic syndrome, diabetes, and cardiovascular disease in ADVANCE trial (abstract #81), CROI 2020 on March 10, 2020.

Hunt CM, Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2. *Hepatol* 2010; 52:2216-2222.

Hunt CM, Papay JI, Stanulovic V, Regev A. Drug rechallenge following drug-induced liver injury. *Hepatology*. 2017 Aug;66(2):646-654.

ICH E2A: International Conference on Harmonisation Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1994).

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. *Drug Metab Dispos* 2009;37(8):1779-1784.

Janssen Document Number EDMS-ERI-198151177. Rilpivirine Population Pharmacokinetics Report. A phase IIIb, randomized, multicenter, parallel-group, non-inferiority, open-label study evaluating the efficacy, safety and tolerability of long-acting cabotegravir plus long-acting rilpivirine administered every 8 weeks or every 4 weeks in HIV-1-infected adults who are virologically suppressed-Study 207966 (ATLAS 2M)-Week 48 Analysis. Effective date: 19-Dec-2019.

Kerchberger AM, Sheth AN, Angert CD, Mehta CC, Summers NA, Ofotukun I, et al. Integrase strand transfer inhibitors are associated with weight gain in women. Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 672, 2019.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et.al. A new equation to estimate glomerular filtration rate. *Ann Int Med*. 2009; 150: 604-12.

McCann K, Moorhouse M, Sokhela S, Daniel W, Venter F, Serenata C, et al. The ADVANCE clinical trial: changes from baseline to week 96 in DXA-assessed body composition in TAF/FTC + DTG compared to TDF/FTC + DTG, and TDF/FTC/EFV. 17th European AIDS Conference, Basel, Switzerland, abstract PS3, 2019

McComsey GA, Eron JJ, Santiago S, Mounzer K, Moyle G, Vanig T, et al. Weight gain during treatment among 3,468 treatment experienced adults with HIV. Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 671, 2019.

McGowan I, Siegel A, Engstrom J, Nikiforov A, Duffill K, Edick S, et al. Persistence of rilpivirine following single dose of long-acting injection. 21st International AIDS Conference (AIDS 2016). July 18-22, 2016. Durban, South Africa. Abstract TUAC0103.

Molina J, Ward D, Brar I, Mills A, Stellbrink H, Lopez-Cortes L, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a raondmised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV*. 2018; 5: e357–65

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. *Regul Tox Pharm*. 2009; 54:84-90.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164:1035–1043.

Rilpivirine Clinical Investigator Brochure (RPV IB), Edition 12, Effective Date: July 2021.

Sato T. On the variance estimator for the Mantel-Haenszel risk difference. *Biometrics*. 1989. *45*(4), 1323-1324.

UNAIDS (2011) Reference Group on Estimates, Modelling and Projections. Working Paper on Mother-to-Child HIV Transmission Rates for use in Spectrum, 6 June 2011. Available online at http://www.epidem.org/Publications/MTCTratesworkingpaper.pdf.

UNAIDS, 2019, Geneva Switzerland, *AIDS Data*

Vallet-Pichar A, Mallet M, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology.* 2007:46(1) 32-36.

Wensig AM, Calvez V, Ceccherini-Silberstein F, Charpentier C, Gunthard HF, Paredes R, et al. IAS-USA 2019 update of the drug resistance mutations in HIV-1. *Top Antivir Med*. 2019;27(3):111-121.

Woodcock A, Bradley C. Validation of the HIV Treatment Satisfaction Questionnaire (HIVTSQ). *Quality of Life Research*. 2001: 10, 517-531.

Woodcock A, Bradley C. Validation of the revised 10-item HIV Treatment Satisfaction Questionnaire status version (HIVTSQs) and the new change version (HIVTSQc). *Value in Health*. 2006: 9(5) 320-333.

World Health Organization (WHO) (2010). Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Recommendations for a public health approach. Available online at: http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf, accessed 6 Feb 2013.

World Health Organization (WHO) (2012). Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 Update. June 2012, Available online at: http://www.who.int/hiv/pub/mtct/programmatic_update_tasp/en/index.html

World Health Organization (WHO) (2013). Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. 30 June 2013. Available online at: http://www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html

Zash R, Holmes L, Diseko M, Jacobson D, Mayondi G. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. JAIDS 2020