TITLE PAGE

Protocol Title: An Open Label, Phase 1 Study to Evaluate the PK, Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, Cabotegravir (CAB; GSK1265744) in HIV Uninfected Chinese Men

Protocol Number: 206898

Short Title: A Phase 1 Safety, Tolerability, Acceptability, and PK study of CAB (GSK1265744) LA in Healthy HIV-Uninfected Chinese Men

Compound Number: GSK1265744

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

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ViiV Implementation Statement

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

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SPONSOR SIGNATORY:

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JUNE 6, 2016
Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	06-JUN-2018
Original Protocol	20-JUL-2017

Amendment 1 [06-June-2018]

Overall Rationale for the Amendment:

This is an amendment to the original protocol.

This amendment has been made to create consistency across protocol sections, and edit wording related to pharmacokinetic sampling for more clarity.

(**Note**: 'Additions' are underlined and 'deletions' are striked off)

Section # and Name	Description of Change	Brief Rationale
2. SCHEDULE OF ACTIVITIES (SoA)	•Drug screen was previous mentioned at footnote '**a**' of SoA table. An additional line of urine drug screen is added to the main table.	•Added for more clarity
	•An additional line of Urine chemistry assessment at day1 is added for baseline assessment	•It is added since, **Appendix 4 Adverse Events**- Proteinuria mentioned that, 'change from Baseline value for abnormal urine microalbumin/creatinine ratio'
	•Additional line for oral phase diary card at day 1.	•Additional assessment
	•Updated footnote '**n**': All PK samples will be collected prior to CAB LA injections at Week 5, 9, 17, 25, and 33 with the exception of 1-week post injection samples at Weeks 6, 10, 18, 26, 34, week 37(~~2~~ 4-week post injection sample) and Week 41	•Updated the schedule PK sampling post injection
5.1. Overall Design	4 ~~PK~~ Pharmacokinetic sampling following CAB LA IM injections will start on just prior to the first injection at Week 5 (Injection Phase) and prior to each subsequent injection with limited PK sampling between injection visits (for complete PK sampling schedule refer to SoA, Table 1).	Added for more clarity
7.1.3. GSK1265744 – Injectable Suspension (CAB LA)	IM injections should be administered at a 90 degree angle into the gluteus medius muscle using a 1.5" – 2.5" 21-25 gauge needle (or sizes outside of this suggested range based on investigator judgement)	Text added around the dimensions of injection needle use for CAB LA injection
7.6. Treatment Compliance	CAB LA dosing is expected to occur in a window ±3 Days ~~any time within the scheduled dose week.~~	Mentioned the specific window period for CAB LA dosing
8.1. Discontinuation of Study Treatment	Participants who discontinue treatment during the injection phase should ~~enter the~~ be followed up ~~phase~~ for at least 56 weeks after their last injection as per	Minor edits for more clarity

Section # and Name	Description of Change	Brief Rationale
	the schedule of activities.	
8.2.2. Withdrawal of Informed Consent	**Added new section with following points:** •If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. •If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. •Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.	Updated separate withdrawal criteria due to withdrawal of Informed consent
9.3. Treatment of Overdose	**Amended** For the Oral Phase of this study, any dose of CAB greater than ~~30 mg~~ 1 tablet (30mg) within a day ~~24 hour time period [±12 hours]~~ will be considered an overdose.	Updated for more clarity
9.5. Pharmacokinetics	**Amended** The last oral dose will be administered on day 28 ~~before~~ after the final PK sample with subsequent safety and central lab assessment on the same day.	Updated the time point for PK sampling
12.2. Appendix 2: Clinical Laboratory Tests	**Under Clinical Chemistry: Added** •Glomerular Filtration Rate (GFR) •Phosphate •Lactate Dehydrogenase (LDH) **Under Urine Chemistry: Added** •Microalbumin	The following tests were mentioned in the protocol, but not listed under Appendix 2

Section # and Name	Description of Change	Brief Rationale
	•Creatinine •Microalbumin/creatinine ratio	
12.2. Appendix 2: Clinical Laboratory Tests	**Other Screening Tests-Deleted** •~~HIV serology (4th generation HIV test)~~ •~~HIV RNA~~	Removed from screening
12.10. Appendix 10: HIV-Prevention Treatment Satisfaction Questionnaire (change): (HIV-PrevTSQc)	**Amended** For the past ~~4 months~~ 10 weeks you have been taking part in a study of treatment to prevent HIV.	To be consistent with SoA table
Throughout	Minor editorial and document formatting revisions Updated the abbreviation table.	Minor, therefore have not been summarized Corrections/clarifications

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1. SYNOPSIS

Protocol Title: An Open Label, Phase 1 Study to Evaluate the PK, Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, Cabotegravir (CAB; GSK1265744) in HIV Uninfected Chinese Men.

Short Title: A Phase 1 Safety, Tolerability, Acceptability, and PK study of GSK1265744 LA in Healthy HIV-Uninfected Chinese Men.

Rationale:

Cabotegravir (CAB, GSK1265744) is an integrase strand transfer inhibitor currently in development for treatment and prevention of HIV infection. CAB has been formulated as a long-acting injectable nanosuspension (CAB LA) with a favorable pharmacokinetic (PK) profile supporting monthly or less frequent administration and the potential to overcome barriers to adherence associated with daily oral antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP). Two regimens of CAB LA (400 mg IM every 4 weeks [Q4W] and 600 mg IM every 8 weeks [Q8W]) are being evaluated in ongoing Phase 2b and 3 treatment studies with long-acting rilpivirine (RPV LA) in HIV infected individuals, both dosing regimens demonstrating efficacy rates >90% for 48-weeks. CAB LA 600 mg IM Q8W, starting 4-weeks following an initial 600 mg IM loading dose, has been selected for evaluation in Phase 3 PrEP studies in uninfected males and transgender females (HPTN083) and in females (HPTN084) at high risk of HIV infection via sexual transmission. These studies will be conducted in the Americas, Africa and in Asian regions excluding China. The PK profile following CAB LA 600 mg IM Q8W observed in healthy and HIV infected individuals achieves concentrations associated with protection against acquisition of Simian/Human Immunodeficiency Virus (SHIV) and Simian Immunodeficiency Virus (SIV) via genital tract challenges in nonhuman primate models and has maintained suppression of HIV in >90% of infected individuals for 48 weeks when coadministered with RPV LA.

This study will evaluate the proposed PrEP regimen in uninfected Chinese male adults at low risk of HIV infection to confirm dosing prior to larger scale PrEP studies in Chinese individuals at high risk of HIV infection. Plasma CAB PK may be impacted by differences in elimination from the systemic circulation and absorption from the injection site. CAB undergoes metabolism primarily by uridine diphosphosphate-glucuronosyltransferase (UGT) 1A1 conjugation. Approximately ~10-15% of the Han Chinese population carry a *6 allele of UGT1A1 which may result in reduced metabolism and ~30-50% higher CAB concentrations than those with wild type UGT1A1. Overall, the impact on average exposure is likely to be less than 10% higher for the Chinese population when compared to other populations. Body morphology and fat distribution may affect absorption of CAB LA from the injection site. Males of lower body mass index (BMI) often exhibit faster absorption and lower trough concentrations than those of higher BMI. Despite potential differences in absorption and elimination in Chinese individuals, the impact on plasma CAB PK is expected to be minimal, and the safety profile of oral CAB and CAB LA offers considerable allowance for any increase in plasma concentrations due to PK differences. This study will confirm dose selection for Phase 3 PrEP studies in Chinese males.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Evaluate the safety and tolerability of the injectable agent, cabotegravir (GSK1265744) long acting (CAB LA) injectable (600 mg dose administered every 4 weeks for 2 doses followed by every 8 weeks for 3 doses) through Week 5-41 in HIV-1 uninfected Chinese men.	Safety and tolerability parameters, including adverse events, clinical laboratory tests, study withdrawals due to AEs, vital signs assessments, and evaluation of injection site reactions (ISRs).
Evaluate the plasma pharmacokinetics of CAB following repeat oral administration (Day 1 to Week 4) and CAB LA IM injections throughout the Injection Phase (Weeks 5-41).	Plasma CAB PK parameters following repeated once daily oral administration (Day1-Week 4) include (as permitted by the data): Cτ, AUC(0-τ), Cmax, tmax, CL/F, Vss, t1/2, and λz. Plasma CAB PK parameters following CAB LA IM administration (Week 5-Week 41) include (as permitted by the data): Cτ, AUC(0-τ), Cmax and tmax.
Secondary	
Evaluate the plasma pharmacokinetics of CAB LA trough the Injection and Long-term Follow-up Phases (Week 5-89)	Plasma CAB PK parameters following CAB LA IM administration (Week 5-Week 89) as permitted by the data including Cτ, AUC(0-τ), Cmax, tmax, CL/F, Vss, t1/2, and λz.
Evaluate the safety and tolerability of oral CAB in HIV uninfected Chinese men during the oral lead-in Phase (Day 1 to Week 4)	Safety and tolerability parameters, including adverse events, study withdrawals due to AEs, vital signs assessments, and clinical laboratory assessments.
Evaluate the acceptability of CAB LA injections through 41 weeks.	Injection discontinuation rate, the number and severity of ISRs and additional acceptability measures.
Explore concentration-effect relationships for various safety and tolerability parameters if relevant.	Evaluation of relationships between significant safety and tolerability parameters and CAB PK may be explored.

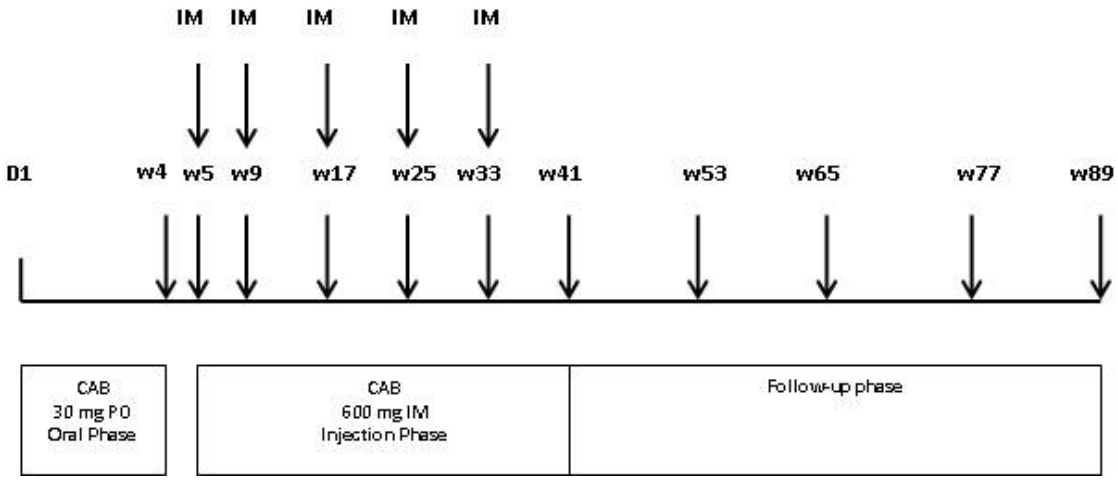
AE: Adverse events, AUC (0- τ): Area under the plasma concentration time curve over the dosing interval, Cτ: Concentration at the end of the dosing interval, Cmax: Maximum observed concentration, Tmax: Time of occurrence of Cmax, τ: Dosing interval, λz: Apparent terminal phase rate constant, CL/F: Oral clearance, Vss: volume of distribution at steady state, t1/2: Terminal absorption elimination half-life

Overall Design:

This is an open label (OL) Phase 1, multi-site, study to evaluate the PK, safety, tolerability, and acceptability of CAB LA in adult HIV uninfected Chinese male participants at low risk for HIV acquisition. Eligible participants will receive both daily

oral CAB and CAB LA. Participants will receive daily oral CAB (30 mg tablets) for 4 weeks during the Oral Phase of the study, to assess for safety and tolerability prior to receiving CAB LA injections. Oral dosing will end and clinical and laboratory safety evaluations will be conducted at Week 4. Following confirmation of safety results from Week 4, participants will enter the Injection Phase at Week 5and receive five CAB LA 600 mg IM injections administered at 8-week intervals, with the first 2 doses given 4 weeks apart, as indicated in below figure. Serial plasma pharmacokinetic sampling over 24 h will be performed before the last oral dose to characterize steady-state PK parameters in an approximately 16 participants. Sparse PK sampling during CAB LA administration will start on the first day of the Injection Phase prior to the first injection and every visit thereafter. Participants will be followed for 56 weeks following their last injection.

206898 Study Schematic



Number of Participants:

Approximately 60 participants will be screened in order to ensure that approximately 48 participants will enter the oral phase and approximately 40 participants will enter the injection phase of the study. Participants will be enrolled from multiple sites in China. Participation will be limited to participants who are male at birth, with a target of at least 60% men who have sex with men.

Treatment Groups and Duration:

Participants will receive daily oral CAB (30 mg tablets) for 4 weeks. Following confirmation of oral CAB safety and tolerability at the Week 4 visit, participants will enter the injection phase and receive CAB LA 600 mg (3 mL) IM injections at the following time points: Week 5, Week 9, Week 17, Week 25 and Week 33. In addition, approximately 16 participants will participate in serial PK sampling at the end of the oral lead in, prior to receiving CAB LA injections.

A participant may withdraw from the 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. Participants that are discontinued prematurely from the injection phase will enter the post treatment period for one year following their last injection unless consent is withdrawn. Study treatment restart or rechallenge after the stopping criteria are met by any participant is not allowed.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 1 SCHEDULE OF ACTIVITIES[q]

Clinical Assessments	Screening[a]	Oral Phase[m]		Injection Phase												Follow-up Phase & Final Visit	
		Day 1	Day 28 (Week 4)	Day 35 (Week 5) Injection 1	Day 42 (Week 6)	Week 9 Injection 2	Week 10	Week 17 Injection 3	Week 18	Week 25 Injection 4	Week 26	Week 33 Injection 5	Week 34	Week 37	Week 41	Week 53, 65, 77	Week 89
Written informed consent	X																
Inclusion/Exclusion criteria[b]	X																
Demographic information	X																
Full physical exam/medical history[c]	X																X
Brief physical exam		X	X	X	X	X	X	X	X	X	X	X	X		X		
Height/weight/BMI[d]	X																X
Medication/drug/alcohol history	X																
HIV counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Offer condoms and lubricant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense oral study medication (with counseling)[e]		X															
Drug accountability (pill counts)		X	X														
CAB LA Injection (with counseling)				X		X		X		X		X					
HIV-PrevTSQc[f]							X										
Oral phase diary card		X															

Clinical Assessments	Screening[a]	Oral Phase[m]		Injection Phase												Follow-up Phase & Final Visit	
		Day 1	Day 28 (Week 4)	Day 35 (Week 5) Injection 1	Day 42 (Week 6)	Week 9 Injection 2	Week 10	Week 17 Injection 3	Week 18	Week 25 Injection 4	Week 26	Week 33 Injection 5	Week 34	Week 37	Week 41	Week 53, 65, 77	Week 89
ISR AE Diary[g]				X		X		X		X		X					
AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE review (SAE will be collected from the signing of ICF)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication check		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[h]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Qualitative HIV RNA by NAAT[i]	X																
HIV PoC test[j]	X	X		X		X		X		X		X			X	X	X
ECG[k]	X																
HbsAg and HbsAb, HCV Antibody	X																
Hematology/Chemistry testing	X	X	X	X	X	X		X		X		X			X		X
Urinalysis	X														X		
Urine drug screen	X																
Urine chemistry		X															
Urine screen for Chlamydia and gonorrhea	X																
Liver Chemistry Tests[l]																X	
Fasting lipid profile		X													X		
Coagulation testing	X														X		

Clinical Assessments	Screening[a]	Oral Phase[m]		Injection Phase												Follow-up Phase & Final Visit	
		Day 1	Day 28 (Week 4)	Day 35 (Week 5) Injection 1	Day 42 (Week 6)	Week 9 Injection 2	Week 10	Week 17 Injection 3	Week 18	Week 25 Injection 4	Week 26	Week 33 Injection 5	Week 34	Week 37	Week 41	Week 53, 65, 77	Week 89
TRUST for Syphilis screen	X																
Plasma for CAB concentration[m,n,o]			X[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma storage sample[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE: Adverse events, BMI: Body mass index, CAB: Cabotegravir, CAB LA: Cabotegravir long-acting, ECG: Electrocardiogram, HbsAg: Hepatitis B surface antigen, HIV: Human Immunodeficiency Virus, HCV: Hepatitis C Virus, ISR: Injection site reactions, SAE: Serious adverse event, HIV-PrevTSQc: HIV-Prevention Treatment Satisfaction Questionnaire (change): TRUST: Toluidine Red Unheated Serum Test, RNA: Ribonucleic acid.

a. Screening (including drug screen) is to be performed within 30 days of the first dose in the Oral Phase of the study. See Appendix 2
b. Inclusion/exclusion criteria will be fully assessed at the Screening visit. Changes between the screening visit and the Day 1 visit should be assessed to ensure eligibility, including additional assessments performed at Day 1.
c. A full physical exam will be performed at Week 89.
d. Weight will be collected at Screening and at Week 89. Height and BMI will be collected at Screening only.
e. Oral phase consists of 28 days with a 7 day washout period between Day 28 (last oral dose) and Day 35 (first injection visit).
f. HIV-PrevTSQc: HIV-Prevention Treatment Satisfaction Questionnaire (change) will be given at Week 10 only (after 2nd injection).
g. ISR AE 7 Day Post Injection Diary will be distributed at the injection visit at Week 5, 9, 17, 25 and 33 and returned to the clinic at weeks 6, 10, 18, 26, and 34. For participants having ISR on the last day of week 5, 9, 17, 25 and 33, additional ISR AE Weeks 2 – 12 Post Injection Diary will be distributed at weeks 6,10, 18, and 26,34. Participants will be asked to bring the diary to each clinic visit.
h. Vital sign measurements will be performed following 5 minutes of rest.
i. Qualitative HIV Nucleic Acid Amplification Testing (NAAT) will be performed at Screening. See Appendix 9 for the HIV testing algorithm at screening, Day 1 and during the course of the study.
j. HIV PoC (Point of care) test will be performed at each time point during the course of the study and must be reviewed prior to IM dosing. See Appendix 9 for the HIV testing algorithm at screening, Day 1 and during the course of the study.
k. ECGs will be performed following 5 minutes of rest in a semi-supine position.
l. Liver Chemistry Tests include Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Bilirubin total and direct.

m. Oral Pharmacokinetic (PK) sampling at trough will be collected for all subjects prior to dose within 20 to 28 hours following oral administration the day prior. Intensive oral PK sampling will be collected from approximately16 participants as shown in Table 2.
n. PK sampling for Injection phase: All PK samples will be collected prior to CAB LA injections at Week 5, 9, 17, 25, and 33 with the exception of 1-week post injection samples at Weeks 6, 10, 18, 26, 34, week 37(4-week post injection sample) and Week 41
o. Long-term follow up PK samples: PK sampling during follow up will occur at, Week 53, 65, 77, and 89.
p. Additional testing is required for participants who have a reactive or positive HIV test after enrolment. Stored plasma from the visit previous to the positive test should be tested for HIV using the 4th generation HIV test to best estimate time of infection. HIV acquisition must be confirmed by either western blot, HIV ½ Multispot or the Geenius HIV Confirmation ½ Assay, and HIV RNA.
q. Visit may occur in a window ±3 Days

Table 2 SCHEDULE OF INTENSIVE ORAL PK APPROXIMATELY 16 PARTICIPANTS) [a,b]

	Day 25	**Day 26**	**Day 27**							**Day 28**	
	Check-in	Oral dose administered (e.g. 8AM)	Prior to oral dose (e.g. 7:55AM)	Oral dose administered (e.g. 8AM)	1-hour post dose (e.g. 9AM)	2-hour post dose (e.g. 10AM)	3-hour post dose (e.g. 11AM)	4-hour post dose (e.g. 12AM)	8-hour post dose (e.g. 4PM)	24-hour post dose (e.g. 8AM)	Oral dose administered (e.g. after 8 AM)
Plasma for CAB concentration			X		X	X	X	X	X	X	

a. PK sampling may occur ± 15min
b. Central lab tests for the intensive oral PK subjects refer to Table 1.

3. INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is a syndrome of immune deficiency caused by human infection with HIV, concurrence of series of opportunistic infections and tumours and leading to death in severe cases.

HIV infection can be transmitted sexually, through blood transfusions, contaminated needles, perinatally, and via breast feeding. High-risk groups include some populations of men who have sex with men (MSM), intravenous drug users, those frequently transfused with unscreened blood and blood products and the infants delivered by HIV-infected mothers.

Cabotegravir (CAB, GSK 1265744) is an investigational HIV integrase strand transfer inhibitor (INSTI) that has attributes favourable for both HIV treatment and prevention indications. CAB is being developed as both oral and long acting injectable formulations. Long-acting antiretroviral agents, capable of being administered on an infrequent basis, may improve adherence to therapy and extend opportunities for effective HIV prevention. Cabotegravir possesses attributes that allow formulation and delivery as a long-acting parenteral (LA) product. These include high-level intrinsic antiviral activity, low systemic clearance, low daily dose requirement, low aqueous solubility, and a high melting point (permitting micronization or nanomilling). To date, results of preclinical and clinical evaluation of CAB as a LA formulation support continued investigation of this approach.

3.1. Study Rationale

Preexposure prophylaxis (PrEP) is an important component in the overall strategy for prevention of HIV infection. Oral tenofovir disproxil fumarate/emtricitabine (TDF/FTC) was recently approved by the United States (US) Food and Drug Administration (FDA) for PrEP and the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have offered interim guidance about TDF/FTC as a PrEP treatment. While the TDF/FTC combination provides an exciting prevention tool, adherence to daily oral therapy as prevention is challenging. Decreased effectiveness has been observed in some randomized placebo-controlled PrEP clinical trials with TDF/FTC when adherence is suboptimal.

CAB LA has been formulated into a long acting therapy. Efficacy in non-human primate models supports its further evaluation as a PrEP therapy in participants at risk of acquiring HIV. As monotherapy, CAB LA may be able to be dosed once every 8 weeks (after 2 monthly loading doses) and is anticipated to provide high level protection by addressing the adherence challenges associated with oral administration.

This study will evaluate the proposed PrEP regimen in uninfected Chinese male adults of low risk of HIV infection to confirm dosing prior to larger scale PrEP studies in Chinese individuals of higher risk of HIV infection. Plasma CAB PK may be impacted by differences in elimination from the systemic circulation and absorption from the injection site. CAB undergoes metabolism primarily by uridine diphosphosphate-glucuronosyltransferase (UGT) 1A1 conjugation. Approximately ~10-15% of the Han

Chinese population carry a *6 allele of UGT1A1 which may result in reduced metabolism and ~30-50% higher CAB concentrations than those with wild type UGT1A1. The impact of differences in metabolism on average exposure is likely to be less than 10% higher for the Chinese population when compared to other populations. Body morphology and fat distribution may affect absorption of CAB LA from the injection site. Males of lower BMI often exhibit faster absorption and lower trough concentrations than those of higher BMI. Despite potential differences in absorption and elimination in Chinese individuals, the impact on plasma CAB PK is expected to be minimal, and the safety profile of oral CAB and CAB LA offers considerable allowance for any increase in plasma concentrations due to PK differences. This study will serve to confirm dose selection for Phase 3 PrEP studies in Chinese males

3.2. Background

The investigational product CAB possesses attributes that permit its evaluation for both HIV treatment and prevention indications. CAB LA is currently in Phase 3 for both the treatment indication (in combination with RPV LA) dosed every 4 weeks (Q4W) and the PrEP indication dosed every 8 weeks (Q8W). Two regimens are being evaluated for treatment, specifically 400mg IM Q4W and 600mg Q8W, both after a beginning 4-weeks oral lead-in period for safety/tolerability assessment followed by administration of long-acting IM injections. The loading dose strategy for both the Q4W and Q8W regimens were modified for Phase 3 studies without change to the corresponding maintenance dose strategy evaluated in Phase 2b; both Q4W and Q8W regimens maintained >90% suppression of HIV for at least 48 weeks.

CAB LA 600mg IM Q8W, starting 4-weeks following a first dose of 600mg IM, was selected for Phase 3 PrEP trials in males and transgender women (HPTN083) and females (HPTN084). Both studies will compare CAB LA to daily oral TDF/FTC to assess any advantage of long-acting administration to overcome adherence challenges associated with oral PrEP. Concentrations following the proposed regimen have been associated with protection in non-human primate models.

Two Phase 2A PreP studies have assessed potential CAB LA regimens for evaluation in Phase 3 PrEP trials. The first was a randomized, placebo-controlled, double-blind, multicenter US study (Study 201120, ECLAIR) in healthy men at low risk of acquiring HIV-1 to assess the safety, tolerability, acceptability, and PK of CAB LA given intramuscularly (IM). Participants were randomized in a 5 to 1 ratio to receive oral CAB 30 mg daily or matching placebo for 4 weeks. Following a safety assessment, participants received three CAB long-acting (LA) 800 mg (2 x 400 mg split IM injection) or saline intramuscular IM injections at 12-week intervals. Most participants (CAB LA, n=106; placebo, n=21) were MSM (83%) and Caucasian (56%). During the injection phase, Grade 2 or higher adverse events were experienced by more participants in the CAB LA group (n=75 [80%]) compared with placebo (n=10 [48%]; $p<0.01$), with the majority attributed to injection-site pain (CAB LA, n=55 participants [59%]; none with placebo). The median duration of injection site pain was 5.4 days. Only 4 participants terminated participation prematurely due to injection intolerability. Geometric mean trough concentrations were lower than predicted and did not achieve the target presumed to offer clinical benefit. Overall, 68 participants (79%) reported willingness to continue

CAB LA injections. In this US study CAB LA injection was well tolerated through Week 41, despite the high incidence of mild-to-moderate injection-site reactions.

HPTN077 (201103), an analogous study to ECLAIR, is an ongoing Phase 2 study evaluating PK and safety of CAB LA in men and women at low risk of HIV acquisition. Two regimens are being assessed in separate cohorts, including 800mg IM Q12W for three doses as well as CAB LA 600mg IM Q8W, with a second dose 4weeks following an initial 600mg IM dose, for a total of five doses. The Q8W regimen was selected based on modeling and simulation that included data from Phase 2 PrEP and treatment studies and was predicted to achieve clinical targets in male and female subjects. This study will evaluate the selected Phase 3 CAB LA 600 mg IM Q8W PreP dosing regimen in Chinese male adults of low risk of HIV acquisition prior to initiating PrEP trials in those of higher risk of infection.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of CAB may be found in the Investigator Brochure [(GlaxoSmithKline Document Number RH2009/00003/06, 2016].

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Drug Induced Liver Injury (DILIs)	A small proportion of participants in the CAB program to date (total exposure approximately 1644 to 01 April 2017) have developed transaminitis (elevated liver transaminases characterized by predominant Alanine aminotransferase [ALT] elevation). In most participants, transient transaminitis was explained by acute hepatitis C infection (majority) and other systemic infections. In a small number of participants, there was not an alternative explanation, suggesting a mild form of DILI without hepatic dysfunction which resolved upon withdrawal of treatment with CAB. Of the four participants with suspected of DILI identified in Phase 2 HIV treatment studies, all were receiving oral CAB.	• Exclusion criteria as described in Section 6.2 will prohibit participants with significant liver impairment based on screening liver chemistry including transaminases (ALT and aspartate aminotransferase [AST]) as well as on prior medical history. Participants with a history of chronic liver disease with ongoing inflammation and/or fibrosis will be excluded. • A 4-week oral lead- in Phase is being implemented in this study, where all participants will receive oral CAB prior to the administration of IM CAB to assess individual tolerance to systemic drug. • Liver transaminases (ALT and AST) will be closely monitored throughout this study (refer to SoA Table 1) and the liver chemistry stopping criteria will be adopted as described in Section 8.1.1 of this protocol. Participants will be withdrawn from CAB treatment where no compelling alternative cause is identified and DILI is suspected. • Participants who develop ALT ≥3 times the upper limit of normal (ULN) while on study must consult with Medical Monitor prior to initiation or continuation of CAB LA.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Injection Site Reactions (ISRs)	Clinical experience to date has demonstrated ISRs occur in the majority of participants receiving CAB LA but are generally mild (Grade 1) or moderate (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days duration (median duration for individual events <1 week). ISRs may occur more than once in an individual participant receiving multiple injections. Although some Grade 3 ISRs were reported, overall ISRs have been well tolerated and have not to date been associated with an excess of participants withdrawing. None of the ISRs reported to date was serious and no clinically significant complications were reported.	• Administration advice will be given to minimize risk of poor administration technique giving rise to injection site reactions. Advice on care, monitoring, natural course, and treatment of ISRs is given in study documentation • Advice will be given to participants on care of injection site on day/days immediately post administration, including 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.
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, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic symptoms associated with use of IM CAB. The long exposures anticipated after IM CAB injection may complicate the management of a drug	• The risk of developing a hypersensitivity reaction post administration of IM CAB will be minimized by the use of a 4-week oral lead-in of oral CAB to determine individual tolerance prior to the introduction of IM CAB. • Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study (refer to SoA Table 1). Results from these assessments may aid early detection of HSR. • Oral CAB will be withdrawn immediately for

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	hypersensitivity reaction, were it to occur.	cases with suspected HSR during the oral CAB lead-in phase and 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.
Development of Resistance following discontinuation of CAB LA	Residual concentrations of CAB LA would remain in the systemic circulation of participants who stopped study product (e.g. for tolerability issues or treatment withdrawal) for varying and in some instances prolonged periods (months). Participants discontinuing a LA regimen may be at risk for developing resistance to CAB many weeks after discontinuing injectable therapy were they to become newly infected with HIV.	• All participants will be provided HIV counseling and testing throughout the study, as well as provision of condoms and lubricant. Additionally, participants will be followed for 56 weeks from the time of the last injection with CAB. Participants who acquire HIV on study will be referred for appropriate care.
Drug-Drug Interactions (DDIs)	For a complete listing of permitted and prohibited concurrent medications for CAB and CAB LA, refer to Section 7.7 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,	• 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**
	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., aluminium, 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 discontinuing injectable therapy.	
Study Procedures		
Risks of ECG pad removal	Participants will be required to have ECG tracings at screening. Some discomfort and rash may occur where the ECG pads are removed.	All ECGs will be conducted by experienced personnel and contact time for the pads on the skin will be kept to a minimum.
Venipuncture as used for blood sample collection	Complications from venipuncture include swelling, bleeding, bruising and infection	• These risks will be minimized using current standard of care techniques for venipuncture.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
Social Harms	Participation in the study could lead to social harms that may include loss of privacy, stigmatization, interference with gainful employment, and coercion. Information regarding social harms will be solicited during every 8 week study visits after enrollment in the study and will be recorded in log form on case report forms (CRFs). In addition, social harms may be identified by other study staff, including recruiters, receptionists, nurses, physicians, pharmacist, and others. All social harms will be brought to the attention of the on-site medical officer and reported according to AE reporting guidelines described in Section 12.4. An investigative committee will review social harm reports and determine appropriate follow-up, including modifying the study protocol and/or procedures as necessary. Participants who report social harms will be referred to speak with a social worker and/or a study counselor.	• Participants who report social harms will be referred to speak with a social worker and/or a study counselor.

3.3.2. Other Clinically Relevant Information

Additional details concerning safety observations from clinical studies and for which a causal association has not been established or which are of minimal clinical significance may be found in the Investigator's Brochure (GlaxoSmithKline Document number RH2009/00003/06 IB Version 6)

Adverse Events of Special Interest:

Seizure
Three cases of seizures have occurred in the CAB program cumulatively through 15 May 2016. Two of the cases occurred in HIV uninfected subjects with a prior history of seizure and one case involved a subject in study 200056 with circumstantial and anecdotal evidence of illicit drug use. Overall, there is not convincing evidence that cabotegravir exposure may be causally associated with seizure or with reduction of seizure threshold, due to the low frequency of reports, the confounders present in the cases received to date and lack of any pre-clinical signal or identified plausible mechanism. However, seizure and seizure-like events are considered as AEs of special interest for close monitoring in future studies. Subjects with recent history of, or recent treatment for seizure or determined to have a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder will be excluded from study participation. For further details refer study reference manual (SRM).

All cases of prior seizure history should be discussed with the Medical Monitor prior to enrolment

3.3.3. Benefit Assessment

Participants in the study will benefit from HIV education and prevention counseling efforts. In addition they will receive access to chemoprophylaxis CAB LA which may be effective in reducing HIV acquisition in adherent individuals. Participants will also be screened for sexually transmitted infections (STIs) and referred for treatment, and receive screening for hepatitis B and C.

3.3.4. Overall Benefit: Risk Conclusion

Safety risks in this study are addressed through study design and careful, long term monitoring. Participants in this study will be at risk, though low, for acquisition of HIV on the basis of the inclusion criteria, and could receive a therapeutic benefit, as well as receiving surveillance of HIV acquisition and other sexually transmitted infections, and will have access to additional prevention counseling. The benefit/risk profile for the continued development of the CAB LA injection and oral formulations as mono-therapy in pre-exposure prophylaxis for horizontal HIV transmission in HIV negative patients remains favorable.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Evaluate the safety and tolerability of the injectable agent, cabotegravir (GSK1265744) long acting (CAB LA) injectable (600 mg dose administered every 4 weeks for 2 doses followed by every 8 weeks for 3 doses) through Week 5-41 in HIV-1 uninfected Chinese men.	Safety and tolerability parameters, including adverse events, clinical laboratory tests, study withdrawals due to AEs, vital signs assessments, and evaluation of injection site reactions (ISRs).
Evaluate the plasma pharmacokinetics of CAB following repeat oral administration (Day 1 to Week 4) and CAB LA IM injections throughout the Injection Phase (Weeks 5-41).	Plasma CAB PK parameters following repeated once daily oral administration (Day1-Week 4) include (as permitted by the data): Cτ, AUC(0-τ), Cmax, tmax, CL/F, Vss, t1/2, and λz. Plasma CAB PK parameters following CAB LA IM administration (Week 5-Week 41) include (as permitted by the data): Cτ, AUC(0-τ), Cmax and tmax.
Secondary	
Evaluate the plasma pharmacokinetics of CAB LA trough the Injection and Long-term Follow-up Phases (Week 5-89)	Plasma CAB PK parameters following CAB LA IM administration (Week 5 - Week 89) as permitted by the data including Cτ, AUC(0-τ), Cmax, tmax, CL/F, Vss, t1/2, and λz.
Evaluate the safety and tolerability of oral CAB in HIV uninfected Chinese men during the oral lead-in Phase (Day 1 to Week 4)	Safety and tolerability parameters, including adverse events, study withdrawals due to AEs, vital signs assessments and clinical laboratory assessments.
Evaluate the acceptability of CAB LA injections through 41 weeks.	Injection discontinuation rate, the number and severity of ISRs and additional acceptability measures.
Explore concentration-effect relationships for various safety and tolerability parameters if relevant.	Evaluation of relationships between significant safety and tolerability parameters and CAB PK may be explored.

AE: Adverse events, AUC (0- τ): Area under the plasma concentration time curve over the dosing interval, Cτ: Concentration at the end of the dosing interval, Cmax: Maximum observed concentration, Tmax: Time of occurrence of Cmax, τ: Dosing interval, λz: Apparent terminal phase rate constant, CL/F: Oral clearance, Vss: volume of distribution at steady state, t1/2: Terminal absorption elimination half-life.

5. STUDY DESIGN

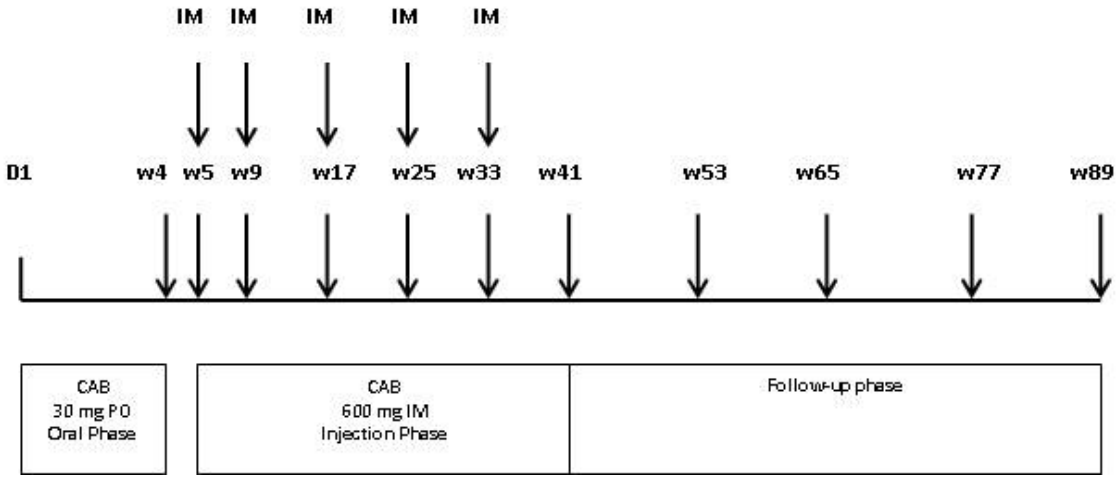
5.1. Overall Design

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns that may arise after the oral administration of CAB. Therefore, adherence to the study design requirements, including those specified in the SoA Table (Table 1), is essential and required for study conduct.

This study is an open label (OL) Phase 1, multi-site, study to evaluate the PK, safety, tolerability, and acceptability of CAB LA in adult male participants (Figure 1). Eligible participants will receive OL CAB LA. Participants will receive daily oral CAB (30 mg tablets) for 4 weeks during the Oral Phase of the study, to assess for safety and tolerability prior to receiving CAB LA injections. Serial PK will also be performed during the oral phase to characterize plasma PK parameters of distribution and elimination. Following safety assessments after 4 weeks of oral dosing, participants will enter the Injection Phase at Week 5 and receive IM injections of CAB LA (Figure 1). CAB LA 600mg will be administered as a single 3-mL IM injection. Subjects who volunteer to participate in the intensive PK assessment will have serial blood sampling for measurement of plasma CAB concentrations following oral administration over a 24 h window starting on Day 27 and ending on Day 28 (Table 2). Pharmacokinetic sampling following CAB LA IM injections will start on just prior to the first injection at Week 5(Injection Phase) and prior to each subsequent injection with limited PK sampling between injection visits (for complete PK sampling schedule refer to SoA , Table 1).

Starting at 8 weeks post last injection, participants will be seen once every 12 weeks for 48 weeks during the follow-up phase.

Figure 1 Study Design



5.2. Number of Participants

Approximately 60 participants will be screened in order to ensure that approximately 48 participants will enter the oral phase and approximately 40 participants will enter the injection phase of the study. The participants will be enrolled from multiple sites in China. Participation will be limited to participants who are male at birth, with a target of at least 60% men who have sex with men. For further details, refer to Section 10.

If participants prematurely discontinue the oral phase of the study, additional replacement participants may be recruited at the discretion of the Sponsor. Participants who enter the injection phase of the study will not be replaced.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including week 89.

The end of the study is defined as the participant completing the week 89 visit.

5.4. Scientific Rationale for Study Design

The currently proposed study will evaluate a CAB LA 600 mg IM Q8W dosing regimen is appropriate, in a Chinese population.

5.5. Dose Justification

Oral CAB 30 mg once daily has been selected as the oral lead-in dose prior to initiating CAB LA IM injections. Following this dose in HIV infected participants, geometric mean Cτ and Cmax were 4.2 µg/mL and 7.5 µg/mL, respectively. Oral CAB 60 mg once daily was safe and well tolerated in Phase 2 treatment studies and achieves geometric mean Cτ and Cmax of 7.9 µg/mL and 12 µg/mL, offering coverage for increased exposures in Chinese males due to any potential decrease in UGT1A1 metabolism. The oral lead-in period will be conducted from Day 1 through Week 4 of the study. Since participants are of low risk of HIV acquisition, oral dosing will be discontinued during safety assessments after the oral lead-in and prior to the first injection at Week 5.

The CAB LA dose rationale is based on the objective of delivering adequate drug concentrations to prevent sexual transmission of HIV. The proposed dose schedule for evaluation in humans is based on maintaining plasma CAB concentrations above the PA-90% of the maximum inhibitory concentration (IC90) value of 0.166 µg/mL which demonstrated a 97% protective efficacy of Simian/Human Immunodeficiency Virus (SHIV) transmission in male macaques. Plasma CAB concentrations >4 x PA-IC90 (0.664 µg/mL) demonstrated 100% protection against intra-rectal SHIV transmission [Andrews, 2014] and was predicted to provide 90% probability of in vivo protection after seven intra-vaginal SIVmac251 challenges in female rhesus macaques [Spreen, 2015].

CAB LA has been administered following single and repeat IM injections to non-HIV infected adult males and females (n=186) and following repeat IM injections to HIV

infected participants (n=230). Relevant PK parameters observed following repeat administration of CAB LA to adults are presented in Table 3.

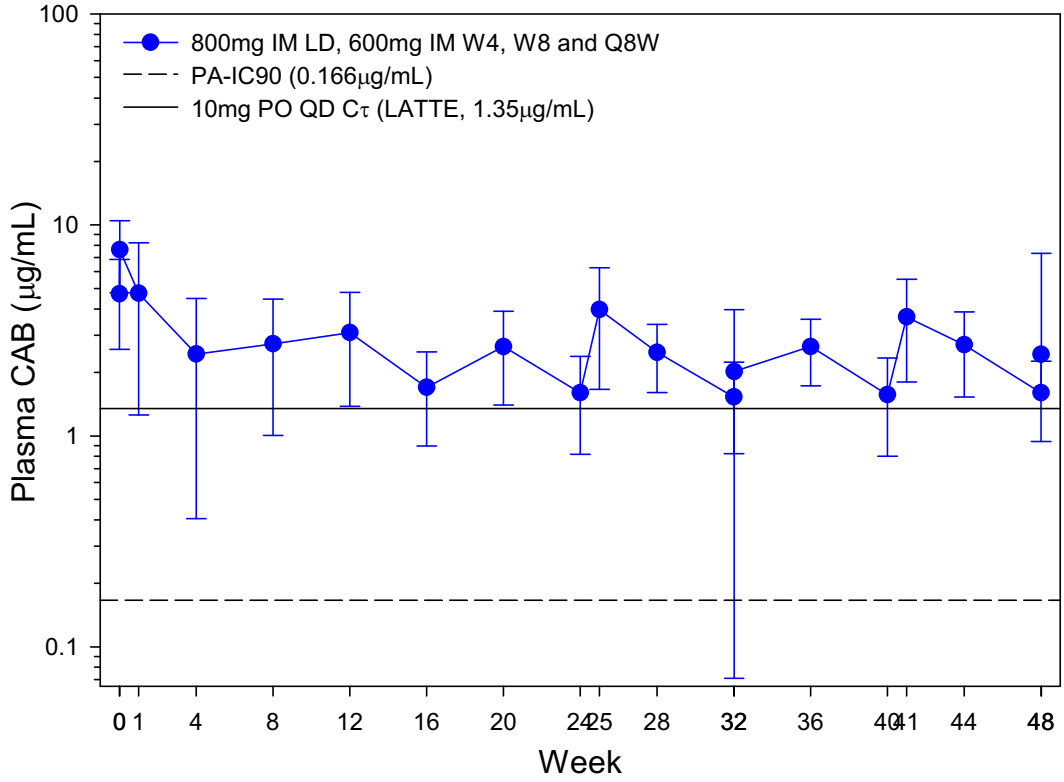
Table 3 Summary of CAB PK Parameters following Repeat Dose Administration of CAB LA to Healthy and HIV-infected Subjects

Population	Study	CAB LA Regimen	Dosing Interval	Plasma CAB PK Parameter (Geometric mean [95%CI] (CVb%)			
				AUC(0- τ) (μg•h/mL)	Cmax (μg/mL)	Cτ (μg/mL)	Tmax[a] (day post last dose)
Healthy Subjects	LAI115428	800 mg IM/ 400 mg IM Q4W (n=10)	D1-W4	1252 [836, 1873] (61)	2.74 [1.72 4.35] (72)	1.78 [1.35, 2.36] (41)	6 (6 – 28)
			W4-W8	2010 [1619, 2494] (31)	3.79 [2.89, 4.99] (40)	2.60 [2.20, 3.07] (24)	6 (2 – 28)
			W8-W12	2182 [1798, 2647] (28)	4.03 [3.05, 5.30] (40)	2.69 [2.21, 3.27] (28)	6 (2 – 28)
			W12-W16	2473 [2063, 2965] (26)	4.41 [3.55, 5.48] (31)	3.27 [2.71, 3.94] (27)	6 (2 – 13)
		800 mg IM Q12W x2 (n=10)	D1-W12	2917 [2045, 4161] (53)	2.70 [1.49, 4.88] (99)	0.74 [0.41, 1.32] (97)	16.5 (2 – 83)
			W12-W24 (n=9)	4468 [3058, 6528] (52)	3.31 [2.18, 5.04] (59)	1.10 [0.50, 2.46] (140)	15 (6 – 42)
	201120 ECLAIR	800 mg IM Q12W x3 (n=93)	D1-W12 (n=93)	3415 [3140, 3714] (42.5)	4.26 [3.64, 4.98] (88.6)	0.302[b] [0.237, 0.385] (157)	7.76 (4.95 – 57.0)
			W12-W24 (n=89)	3873 [3543, 4235] (44.3)	5.22 [4.52, 6.04] (78.0)	0.331[c] [0.253, 0.435] (165)	6.97 (3.83 – 75.0)
			W24-W36 (n=85)	4021 [3728, 4337] (36.2)	4.91 [4.31, 5.60] (66.6)	0.387[d] [0.296, 0.505] (150)	6.99 (5.63 – 43.0)
HIV Infected Subjects	200056 LATTE2	800 mg IM/ 400 mg IM Q4W (n=115)	W24-W28 (n=97)	1858[e] [1719, 2007] (37)	3.50 [3.2, 3.8] (39)	2.35[f] [2.2, 2.5] (32)	6.9 (0 – 29)
			W40-W44 (n=95)	2017[g] [1847, 2203] (41)	3.50[j] [3.3, 3.8] (37)	2.56[h] [2.4, 2.7] (32)	6.9 (0 – 28)
		800 mg IM/ 600 mg IM Q8W (n=115)	W24-W32 (n=98)	3037[i] [2786, 3310] (42)	3.55 [3.2, 3.9] (56)	1.43[j] [1.3, 1.6] (54)	6.9 (0 – 59)
			W40-W48 (n=104)	3027[k] [2762, 3322] (47)	3.33 [3.1, 3.6] (47)	1.49 [1.4, 1.6] (42)	7.0 (0 – 57)

a. median (range)
b. n=84
c. n=71
d. n=66
e. n=84
f. n=108
g. n=80
h. n=98
i. n=86
j. n=100
k. n=112

PK data from the ECLAIR (201120) study showed only 30 to 37% of reportable CAB plasma trough concentrations were ≥4x PA-IC90 following each of the three injections, and 15 to 31% were below 1x PA-IC90 [Markowitz, 2016]. Graphical evaluation of the CAB concentration-time profiles suggests that absorption was more rapid among participants in the ECLAIR study than predicted, resulting in higher peak and lower trough concentrations. In the LATTE-2 (200056) study, CAB LA was evaluated in combination with Rilpivirine (RPV) LA at two dosing frequencies Q4W and Q8W. The Q8W regimen included an 800 mg loading dose and two subsequent monthly doses of CAB LA 600mg prior to initiating an every 8-week dosing interval starting at Week 8. On average, this Q8W regimen achieved clinical targets in both males and females (Figure 2), supporting the selection of an every 8-week regimen for PrEP.

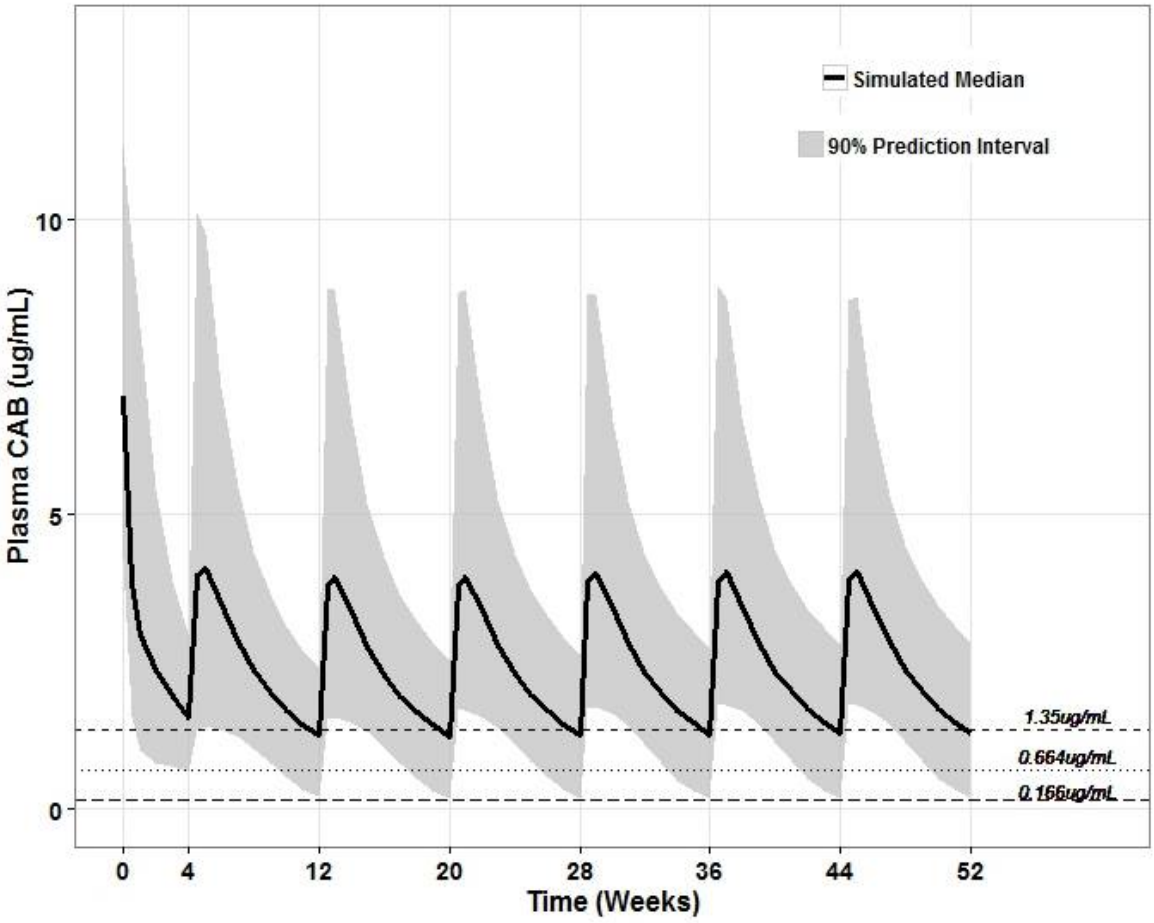
Figure 2 Observed Mean (SD) Concentration-Time Data following CAB LA Q8W in HIV infected subjects (200056 (LATTE-2)



A population PK analysis has been performed to select doses for study in Phase 3 trials in treatment and PrEP using NONMEM 7.2 (ICON Development Solutions, Ellicott City, Maryland, USA) with data from eight Phase 1 and 2a studies plus the two Phase 2b studies 201120 (ÉCLAIR) and 200056 (LATTE-2). A total of 416 participants provided data following CAB LA IM administration, with approximately 50% of data obtained from LATTE-2, ~20% from ECLAIR and ~30% from Phase 1/2a studies. A two-compartment model with first order absorption characterized the observed data well. High BMI (>30 kg/m^2) and female sex were associated with slower absorption rates. BMI and formulation change helped explain a minor amount of the variability of KA LA. Scaling of central volume and systemic clearance by weight also improved model fit. Model performance was assessed using various goodness-of-fit criteria, including a visual inspection of diagnostic scatter plots, successful minimization, completion of covariance step, and precision of the parameter estimates. A visual predictive check was used to validate the model.

The model was used to simulate the median (90% prediction interval (PI)) CAB concentration-time profile for the selected CAB LA PrEP regimen of 600mg IM Day 1, Week 4, then Q8W. The simulated profile for this regimen for male participants is shown in Figure 3. At steady state, 50% are predicted to achieve trough concentrations above the geometric mean trough following the 10 mg oral dose of 1.35µg/mL (8-fold PA-IC_{90}), which was shown to be efficacious in maintaining viral suppression when coadministred with in RPV 25mg once daily in LATTE, and 95% are predicted to achieve trough concentrations above PA-IC90. A one week delay in dosing of 600mg IM at steady state resulted in a drop in the median $C\tau$ to 1.08µg/mLwith 92% of $C\tau$ values remaining above the PA-IC90, supporting a maximum one week delay in dosing. Phase 3 PrEP trials with the selected CAB LA dose have started in late 2016.

Figure 3 Simulated* Median (90% Prediction Interval [PI]) Plasma CAB Concentrations versus Time for the Selected CAB LA Q8W Regimen (600 mg IM Day 1, Week 4, then Q8W) in Male Subjects with normal UGT function



Above simulation includes oral lead-in dosing up to and includeing the day of the first injection. In this study, however, there will be an approximately 1-week washout between the last oral dose and the first injection at Week 5.

Although race is not a significant covariate, Asian participants comprise only ~2.5% of the IM data in the current population pharmacokinetic (PK) model. Variability in the CAB LA profile is driven by absorption rate constant (which is impacted by gender and BMI) and systemic clearance, which can be affected by metabolic pathways and body size measures (weight). Adult Asian males are assumed to be similar in size to those in the model. Differences in UGT metabolism may, however, play a role in disposition of CAB LA in Asian participants.

Metabolism of CAB primarily involves UGT1A1, with a minor contribution from UGT1A9. Carriage of the UGT1A1 *28 (common) and *37 (African ancestry), and *6 (East Asian populations) alleles results in decreased UGT1A1 enzyme activity compared to wild type enzyme activity (UGT1A1 *1/*1 [Barbarino, 2014]. The clinical impact of reduced UGT1A1 enzyme activity varies between medicines. Reduced UGT1A1 enzyme

activity is associated with significant changes in disposition of irinotecan and its metabolites and, consequently, increased risk of treatment-induced toxicities [Stingl, 2014; Fujita, 2010]. In contrast, carriage of UGT1A1 polymorphisms that reduce enzyme activity have a modest effect on the oral integrase inhibitor (INI) dolutegravir exposure and its safety [Chen, 2014].

The UGT1A1*28 polymorphism has been reported to be associated with hyperbilirunemia induced by several drugs, is known to cause reduced UGT1A1 expression and predisposes individuals to Gilbert's syndrome, a benign form of episodic jaundice [Bosma, 1995; Raijmakers, 2000; Danoff, 2004; VOTRIENT Package Insert 2015, TASIGNA Package Insert, 2015]. Mild (grade 1 to 2), nonprogressive bilirubin (TBL) increases observed in a small subset of patients in LATTE might be a consequence of cabotegravir acting as a substrate of UGT1A1 [Margolis, 2015].

A pharmacogenetic (PGx) study was undertaken to evaluate the effect of *UGT1A1* and *UGT1A9* genotypes on exposure and tolerability in participants receiving oral CAB in six studies. The PGx analysis specifically examined 1) PK measurements from participants in Phase 1 and 2 studies treated with oral CAB 30 mg once daily for at least 8 days; and 2) selected tolerability endpoints using participants treated with oral CAB from a Phase 2 study.

Genetically predicted UGT1A1 activity was significantly associated with steady-state oral CAB 30mg PK parameters Cτ, AUCτ, and Cmax, with mean values of Cτ, AUCτ, and Cmax ~1.5, 1.4 and 1.3-fold, respectively, higher in participants with low relative versus normal predicted activity. Based on the cumulative CAB PK and safety data collected to date, this magnitude of increase in CAB exposure is not anticipated to have a clinically relevant impact and does not change the understood benefit-risk profile of 30mg oral CAB.

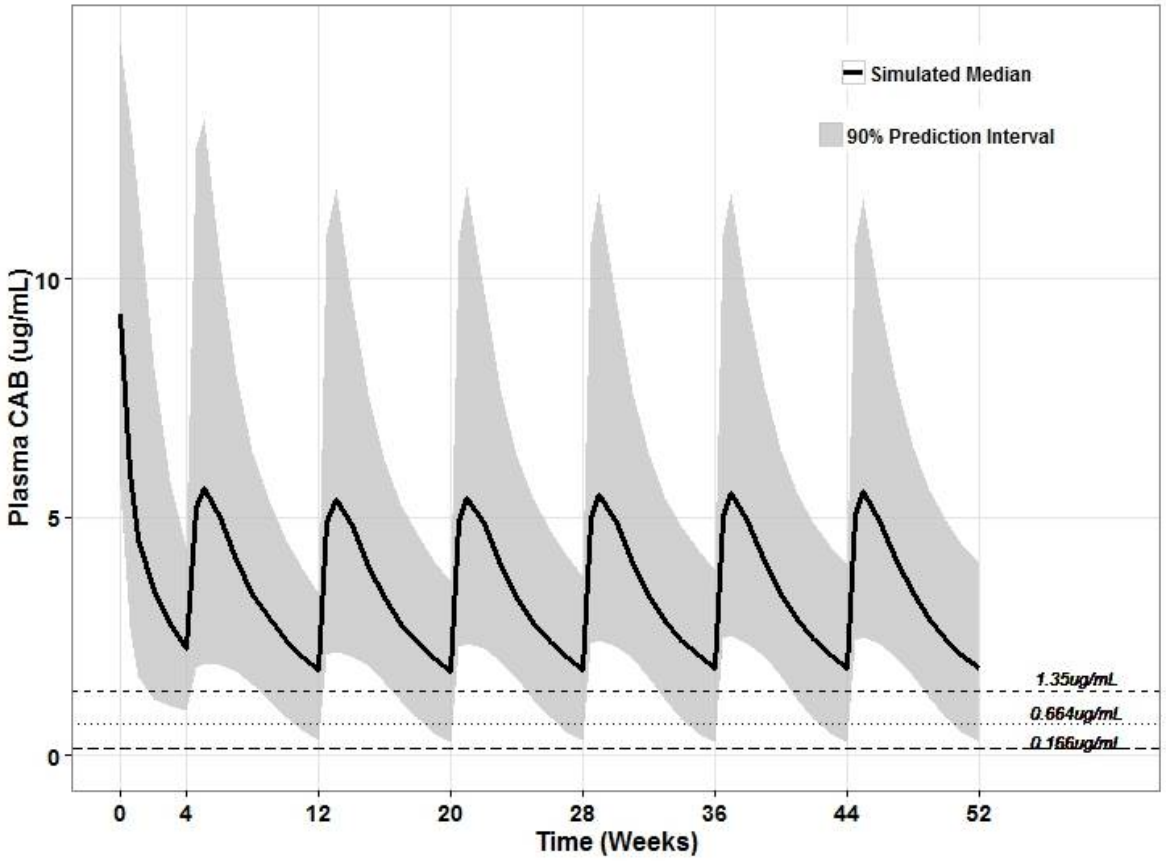
Genetically predicted UGT1A1 activity was significantly associated with change from baseline TBL, but not ALT. None of the five participants who had maximum on-treatment TBL≥1.5xULN in this dataset, had genetically predicted normal UGT1A1 activity; all carried one or more reduced function UGT1A1 alleles.

The UGT1A9 genetic variant (*1B) was not associated with any PK endpoints analyzed or with maximum on-treatment ALT, but was moderately associated with maximum on-treatment TBL. After accounting for genetically predicted UGT1A1 activity within the same model, UGT1A9 *1B is no longer significantly associated with change from baseline TBL, which suggests that the association between UGT1A9 and TBL may be due to the correlation between UGT1A1 and UGT1A9. Further details of the Pgx analysis are provided in Section 27.4 of the China Investigational New Drug (IND).

Based on the pharmacogenetics analysis, a 1.4-fold increase in AUC (0- τ) would correspond to a ~30% reduction in CL. Therefore, participants carrying a *6 allele (~10-15% in Han Chinese population) are predicted to have higher CAB concentrations following CAB LA than those (of same size and gender) with wild type UGT1A1. Simulated median (90% PI) of the proposed PrEP regimen in male participants with reduced UGT function (30% decreased CL) is shown in Figure 4. Median predicted

steady state Cτ has increased from 1.35 µg/mL to 1.8 µg/mL. The median predicted steady state Cmax (1-week post injection concentration) increased from 4 µg/mL to 5.5 µg/mL, and the 95th percentile from 8.7 µg/mL to 11.8 µg/mL, within the range studied following oral CAB in HIV infected participants (LATTE). Given the overall good tolerability and safety profile of CAB, it is unlikely that any increase in concentrations will produce AEs. However, there may be a predisposition to increased liver function tests (total bilirubin) in those carrying the genetic variants.

Figure 4 Simulated* Median (90% Prediction Interval [PI]) Plasma CAB Concentrations versus Time for the Selected CAB LA Q8W Regimen (600 mg IM Day 1, Week 4, then Q8W) in Male Subjects with Reduced UGT Function



6. STUDY POPULATION

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns that may arise after the oral administration of CAB.

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 Investigator's Brochures (IB) for CAB (GlaxoSmithKline Document Number RH2009/00003/06, 2016).

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.

6.1. Inclusion Criteria

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

AGE
1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent
TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Participants are male at birth 3. Participants who have non-reactive POC HIV test and undetectable HIV-1 RNA at screening. 4. At risk of acquiring HIV, defined as having at least one casual male or female sex partner in the past 24 months 5. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring at the time of screening;
INFORMED CONSENT
6. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
OTHER
7. Agree to appropriate use of contraceptive measures during heterosexual intercourse. • All participants should be counselled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) to reduce the risk of sexually transmitted infections. 8. Willing to undergo all required study procedures

6.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION)
1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 2. History of the following cardiac diseases: myocardial infarction, congestive heart failure, documented hypertrophic cardiomyopathy, sustained ventricular tachycardia. 3. Active skin disease or disorder (i.e., infection, inflammation, dermatitis, eczema, drug rash, psoriasis, urticaria). Mild cases of localized acne or folliculitis or other mild skin condition may not be exclusionary at the discretion of the Investigator of Record or Medical Monitor. 4. 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. 5. Any medical condition, including psychiatric conditions that in the judgment of the investigator would interfere with the participant's ability to complete study procedures. 6. Participant who, in the investigator's judgment, poses a significant suicide risk.
CONCOMITANT MEDICATIONS
7. Use of antiretroviral (ARV) therapy (e.g., for Post exposure prophylaxis [PEP] or PrEP) in the past 30 days. 8. Use of high dose aspirin or any other anticoagulant or antiplatelet medication that would interfere with the ability to receive IM injections.
RELEVANT HABITS
9. Assessed by the Investigator of Record or designee as being at "high risk" for HIV infection. This may include one or more of the following: • The negative partner in an HIV serodiscordant couple where the HIV infected partner is not suppressed. • Men who exchange sex for goods or money. • Men who have engaged in any condomless anal intercourse within the past 6 months. • Men who have had greater than 5 male or female sexual partners within the past 6 months • Men who have had a sexually transmitted disease within the past 6 months. • Any other behaviour assessed by the investigator as "high risk". 10. History of drug or alcohol consumption that in the opinion of the Principal Investigator will interfere with study participation.

11. Ongoing intravenous drug use – episodic use or any use in the past 90 days is exclusionary (as assessed by the study investigator).
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
12. One or more reactive HIV test results at screening or enrolment, even if HIV infection is not confirmed. Negative HIV RNA must also be documented at screening. 13. Co-enrolment in any other HIV interventional research study (provided by self-report or other available documentation) or prior enrolment and receipt of the active arm (i.e., NOT a placebo) of a HIV vaccine trial (provided by available documentation). 14. Any of the following laboratory values during the screening period: • Positive Hepatitis C antibody result • Positive Hepatitis B surface antigen (HBsAg) • Hemoglobin <11 g/dL • Absolute neutrophil count <750 cells/mm^3 • Platelet count ≤100,000 cells/mm^3 • Presence of a coagulopathy as defined by an international normalized ratio(INR)>1.5 or a partial thromboplastin time (PTT) >45sec • Calculated creatinine clearance <60 mL/minute using the Cockcroft-Gault equation • A single repeat test is allowed during the Screening period to verify a result, with the exception of HIV tests. 15. Participants with an alanine aminotransferase (ALT), alkaline phosphatase (ALP) or bilirubin ≥1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 16. The participant has a tattoo or other dermatological condition overlying the gluteus region which may interfere with interpretation of injection site reactions .

6.3. Lifestyle Restrictions

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory test.

6.4. Screen Failures

Participants who do not meet all inclusion, exclusion and any other eligibility criteria will be considered Screen Failures. Basic study data will be collected for all screened participants including the reason for screen failure to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Participants are allowed to rescreen once but the participant will be assigned a new participant number. Participants who are administered oral CAB (or oral phase) and subsequently withdrawn from the study, for any reason, may not be re-screened.

7. TREATMENTS

Study treatment is defined as any investigational treatment intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

7.1.1. Study Treatments

Table 4 Study Treatments

Study Treatment		
Product Name:	Oral CAB	CAB-LA
Dosage Formulation	Tablet	Sterile Suspension for Injection Vial
Unit dose strength(s)/Dosage level(s):	30 mg tablet Dose level = 1 tablet	200 mg/mL sterile suspension Dose level = 600 mg (3 mL)
Route of Administration	Oral	Intramuscular injection
Dosing instructions	Administer orally, once daily. Dose at same time daily without regard to food with water	Intramuscular Injection. See instructions in Study Reference Manual (SRM) for preparation and administration
Packaging and Labeling	Study Treatment will be provided in high density polyethylene (HDPE) container. Each container will be labeled as required per country requirement.	Study Treatment will be provided in USP Type I glass vial with a 13 mm gray stopper and an orange colored plastic flip off overseal. Each vial will be labeled as required per country requirement.

USP United States Pharmacopeia

7.1.2. GSK1265744 – Tablet (CAB)

The investigational product (IP) CAB is manufactured by GlaxoSmithKline (GSK) and is formulated as white to almost white oval shaped film coated 30 mg tablets for oral administration, packaged in HDPE bottles with child-resistant closure that include an induction seal. The CAB tablets will be packaged in bottles containing 30 tablets each. Participants must keep all IP in its original package container. CAB tablets are to be stored up to 30°C and protected from moisture.

7.1.3. GSK1265744 – Injectable Suspension (CAB LA)

The IP CAB LA is manufactured by GSK and is a sterile white to slightly colored suspension containing 200 mg/mL of CAB as free acid for administration by IM injection. The product is packaged in a 3 mL USP Type I glass vial with a 13 mm gray stopper and an orange colored plastic flip off overseal. Each vial is for single use

containing a withdrawable fill of 2.0 mL, and does not require dilution prior to administration. CAB LA injectable suspension is to be stored at up to 30°C, do not freeze. Participants will be assigned to study treatment in accordance with the schedule mentioned in SoA (Table 1).

Vials of CAB LA are supplied as a suspension and need no further dilution or reconstitution. However, sites should gently invert the vials 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. The time of injection will be captured in the electronic case report form (eCRF).

IM injections should be administered at a 90 degree angle into the gluteus medius muscle using a 1.5" – 2.5" 21-25 gauge needle (or sizes outside of this suggested range based on investigator judgement). The needle should be long enough to reach the muscle mass and ensure an IM injection, but not so long as to involve underlying nerves, blood vessels, or bone. Longer needle lengths will be required for participants with higher BMIs, to ensure that injections are administered intramuscularly as opposed to subcutaneously. BMI, needle gauge, and length will be collected in the eCRF.

For participants with a higher BMI the investigator should consider using a longer needle, see SRM for details.

In the event of suspected intravenous administration, a PK sample will also be drawn approximately 2 hours post dose for evaluation of CAB plasma concentrations. Detailed dosing instructions can be found in the SRM.

7.2. Dose Modification

Dose modification will not be permitted in this study. Data from this study may be the basis of future dose modifications for subsequent studies.

7.3. Method of Treatment Assignment

This will be an open label, non-randomized, single arm study. Participants will receive daily oral CAB (30 mg tablets) for 4 weeks during the Oral Phase of the study and IM injections of 600 mg of CAB LA at Week 5, Week 9, Week 17, Week 25 and Week 33 during the Injection phase. For details of dosing refer to Section 2.

7.4. Blinding

This will be an open label, non-randomized, single arm study.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Take adequate precautions to avoid direct eye or skin contact. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- 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.

7.6. Treatment Compliance

- When participants are dosed at the site, they will receive study treatment 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 treatment 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 treatment.
- During the oral dosing phase, compliance will be assessed through querying the participant during the site visits and documented in the source documents and CRF. A record of the number of CAB tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.
- CAB LA 600 mg at weeks 5, 9 and every 8 weeks up to 33 weeks will be intramuscularly administered to participants at the site. Administration will be documented in the source documents and reported in the CRF.

Note:

- CAB LA dosing is expected to occur in a window ±3 Days

- CAB LA dosing may occur without consultation from the medical monitor if performed within this dosing window.

Any request for dosing to occur outside of the dose week 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.

7.7. Concomitant Therapy

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

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

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

7.7.1. Permitted Medications and Non-Drug Therapies

Not applicable.

7.7.2. Prohibited Medications and Non-Drug Therapies

Experimental agents not otherwise specified in the protocol, cytotoxic chemotherapy, antiretroviral therapy, or radiation therapy may not be administered. Systemically administered immunomodulators are prohibited.

The following medications could significantly decrease the levels of CAB in the blood due to enzyme induction and therefore must not be administered concurrently:

- carbamazepine
- oxcarbazepine
- phenobarbital
- phenytoin
- rifabutin
- rifampin
- rifapentine
- St. John's wort

The following medications are anticoagulant/antiplatelet medications and could interfere with the ability to receive intramuscular injections. Their use is prohibited within 7 days before and for 7 days after the injection:

- high dose aspirin
- anagrelide
- apixaban
- argatroban
- bivalirudin
- clopidogrel
- dabigatran
- dalteparin
- enoxaparin
- fondaparinux
- heparin
- lepirudin
- prasugrel
- rivaroxaban
- ticagrelor
- ticlopidine
- warfarin

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment after completion of the study.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants who discontinue study treatment during the oral phase will be withdrawn from the study. Participants who discontinue treatment during the injection phase should be followed up for at least 56 weeks after their last injection as per the schedule of activities.

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

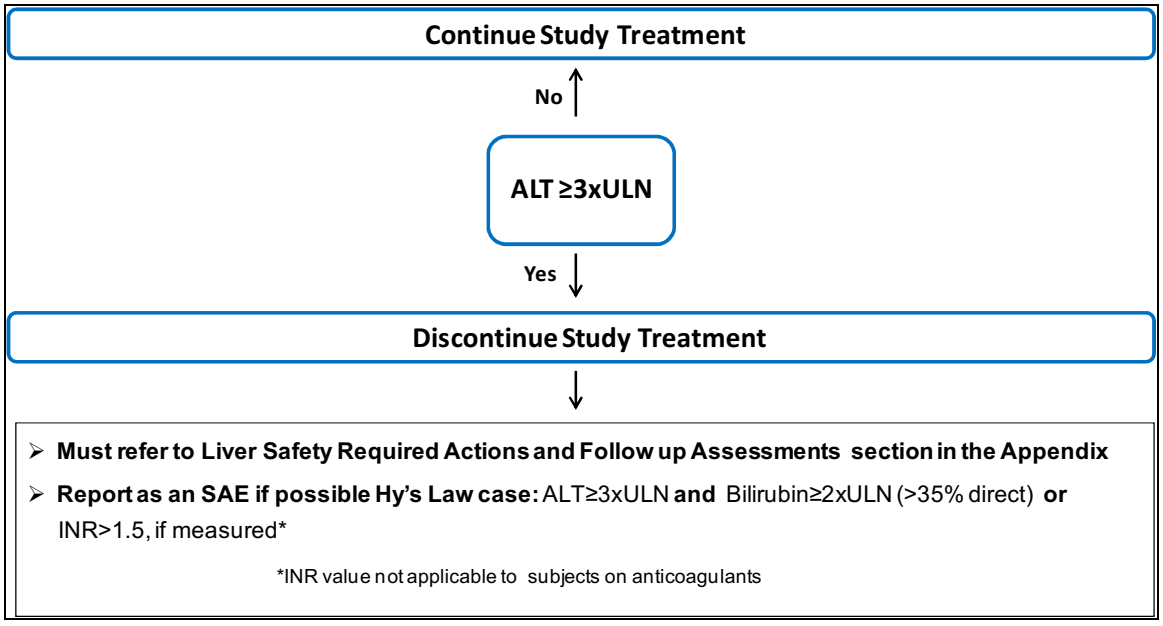
Discontinuation of study treatment for abnormal liver tests is required when

- a participant meets one of the conditions outlined in the algorithm

or

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the

best interest of the participant **Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm**



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6 .

8.1.2. Temporary Discontinuation

Temporary discontinuation is not allowed.

8.1.3. Follow up visits for participants withdrawn from IM dosing

Participants that are withdrawn from study treatment will continue to be followed for 56 Weeks. All participants who have received at least 1 injection will be followed as per the follow-up phase of the study. Starting eight weeks post last injection, participants will be seen once every 12 weeks for up to 48 weeks.

At each visit the following long term follow up procedures will be performed:

- HIV POC test
- HIV counselling
- Offer condoms and lubricant
- Adverse event and SAE review
- Concomitant medication review
- Liver function tests
- Plasma sample for drug level
- Plasma sample for storage

Final visit will be performed at 56 weeks post last injection (see Section 2) Week 89.

8.1.4. Rechallenge

8.1.4.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after the stopping criteria are met by any participant participating in this study is not allowed.

8.2. Withdrawal from the Study

8.2.1. Withdrawal from the Study Treatment

A participant may withdraw from the 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. Participants that are discontinued from treatment during the Oral Phase will end their participation at that time. Participants that are discontinued from treatment during the Injection phase will enter the post treatment period unless consent is withdrawn. All participants who have received at least 1 injection of CAB LA will be followed as per the follow-up phase of the study. Starting eight weeks post last injection, participants will be seen once every 12 weeks for up to 48 weeks. Every effort should be made to complete the early termination study procedures and observations if the participant does not enter post-treatment follow-up.

Any laboratory parameter that meets the stopping criteria should be repeated once to confirm the value prior to withdrawal

Reasons for study treatment discontinuation during the Oral or Injection Phase may include:

- Confirmed HIV acquisition
- Any clinically significant AE deemed to require discontinuation of investigational product
- Grade 3 or higher rash or Grade 2 rash with evidence of systemic involvement
- Grade 2 or higher allergic reaction
- Post entry co-enrolment in an HIV prevention study
- Use of PrEP during the course of the study
- Behaviors assessed by the investigator as being at “high risk” for HIV infection during the course of the study

These thresholds assume that participants are asymptomatic with respect to these changes. In the presence of clinically significant symptoms, lower thresholds for these parameters may need to be used for consideration of possible withdrawal of participants from the study treatment, after consultation between the Principal Investigator and a Medical Monitor.

Before discontinuing a participant from investigational product(s), the Investigator must contact the Medical Monitor. In the event that the investigator is unable to reach the

Medical Monitor, the Investigator, at his or her discretion, may withhold investigational product(s) from a participant until the Medical Monitor or designee can be contacted.

8.2.2. Withdrawal of Informed Consent

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

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

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2)
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Sites will follow the HIV testing algorithm for Screening detailed in Appendix 9 and included in the SRM. If a reactive/positive result is obtained for any HIV test, the person is not eligible for the study. Additional testing to confirm suspected HIV infection during Screening will be performed in accordance. Participants with reactive screening tests for HIV will receive counselling and be referred for further testing and appropriate management.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of Informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Table 1).
    - The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 1500 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

In this study only pharmacokinetic and safety parameters will be evaluated, efficacy assessment is not applicable.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any 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 treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

Seizures or suspected seizures are to be reported to GSK promptly (within 24 hours of learning of the event) for evaluation and possible onward reporting (see Section 3.3.2). Any seizures and suspected seizures that meet the definition of an AE or SAE should be reported in these forms.

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

- All SAEs will be collected from the signing of the ICF until the final follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until the final follow-up visit at the time points specified in the SoA (Section 2).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section, unless it is an SAE.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs 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 to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AE and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

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:

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 12.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment 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 Serious adverse event (SAE) or other specific safety information (e.g., summary or listing of SAE) 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.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF 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 Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF 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.

9.3. Treatment of Overdose

For the Oral Phase of this study, any dose of CAB greater than 1 tablet (30 mg) within a day will be considered an overdose. For the Injection Phase, any dose of CAB LA greater than 600 mg will be considered an overdose. GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose In the event of an overdose, the investigator or treating physician should:

1. Contact the Medical Monitor immediately.
2. For oral overdose, closely monitor the participant for AE/SAE and laboratory abnormalities (at least 14 days). For injection overdose monitor the participant for AE/SAE and laboratory abnormalities as per the SoA.
3. For oral overdose, obtain a plasma sample for PK analysis within 14 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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the (Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological) systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum assessments of the (Skin, lungs, cardiovascular system, and abdomen [Liver and spleen]).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Injection site reaction

Injection site reactions will be recorded via ISR diaries and 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.

9.4.3. HIV Counseling

Participants will be assessed for HIV risk behaviors at each visit and should be provided with risk-reduction counseling. This should also include assessing sexually transmitted diseases symptoms (testing and treating to be applied, as needed). If a significant change in risk from baseline is identified during the study, the investigator should discuss continuing participation with the medical monitor. Participants with documented risk behaviors requiring the use of PEP should have study treatment withdrawn and managed as per Section 8.2.

9.4.4. Acquisition of HIV During the Study

A participant with a positive POC test will have additional samples collected at the same visit to confirm the acquisition of HIV. A confirmatory test either western blot, HIV ½ Multispot or the Geenius HIV Confirmation ½ Assay, and HIV RNA will be performed. Further information on interpretation is available in the SRM. Participants who become HIV-infected during the course of this study will be referred to care. It is the responsibility of the principal investigator to refer the HIV positive participant to an appropriate center for HIV care. Investigator will guide HIV positive participants to start suppressive HIV treatment as soon as possible to minimize the risk of development of drug resistance. A post-HIV confirmation visit will be scheduled and procedures will be performed as outlined in Appendix 5. Participants who become infected with HIV-1 during the Injection Phase should enter the follow-up phase and be managed as per Section 8.2.

9.4.5. Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate and respiratory rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.

9.4.6. Electrocardiograms

A single 12-lead ECG will be obtained at screening as outlined in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT interval (QTc) intervals.

9.4.7. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after last dose of oral study treatment or 56 weeks following their last injection, 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 aetiology should be identified and the sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- Blood plasma samples for storage will be collected as indicated in the Section 2 (SoA). Stored plasma will also be collected from participants who acquire HIV infection, these assessments include: CAB PK measurements, CD4 count, Viral Load, resistance testing, HIV sub typing, characterization of the virus and/or the host response to infection. As these assessments will be performed retrospectively; results will not be returned to study sites or participants. An HIV confirmatory visit will be scheduled (Appendix 5).

9.5. Pharmacokinetics

- Intensive oral CAB PK will be measured in approximately 16 subjects. These subjects will spend three continuous nights at the clinic. Subjects will check in on Day 25 and will take the Day 26 oral dose (e.g. 8 AM) at the clinic. Sample collections on Day 27 following oral dose (e.g. 8 AM) at the clinic. Sample collections on Day 27 following observed oral CAB dosing in the clinic will be obtained before oral dose (e.g. 7:55 AM), and following dose administration at 1, 2, 3, 4, 8 -hour post-dose and on Day 28, 24-hour post the Day 27 dose Approximately 2mL of blood samples will be collected at each of these time points. The last oral dose will be administered on day 28 after the final PK sample with subsequent safety and central lab assessment on the same day. For study subjects not participating in the intensive PK part of the study, they will come in only for day 28 visit for pre-dose PK sampling (approximately 20 to 28 hours after the dose taken at home the day prior) as well as safety and central lab assessment.

- Blood samples will be processed to harvest plasma within 1hr of sample collection. Samples collected for analyses of study treatment, plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

- Determination of CAB concentration in plasma will be performed in Covance Pharmaceutical R&D (Shanghai) Co., Ltd under the monitoring of GlaxoSmithKline. CAB concentrations will be determined in plasma using an approved, validated analytical methodology. A method validation report will be generated to demonstrate the details in validation assessments.
- Once the plasma has been analyzed for CAB, any remaining plasma to be used may be analyzed for other compound-related metabolites and the results reported under a separate protocol.
- All pharmacokinetic analyses will be performed under the direction and supervision of the Antiviral Group of Clinical Pharmacology Modelling and Simulation (CPMS) at GlaxoSmithKline. Individual plasma PK parameters will be determined by non-compartmental methods using WinNonlin Professional 5.2 or higher, Phoenix (Certara Corporation) or comparable software.

- PK parameters following oral administration may include area under the plasma concentration time curve over the dosing interval (AUC [0-τ]), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at the end of the dosing interval (Cτ), oral clearance (CL/F) and steady state volume (Vss). Following CAB LA administration, individual plasma PK parameters for specific injection intervals of the Week 5-41 injection phase of the study will be determined where applicable, and may include: area under the plasma concentration time curve over the dosing interval (AUC [0-τ]), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at the end of the dosing interval (Cτ), and apparent terminal phase half-life for CAB LA administration (t½) and lambda z as a measure of absorption rate constant (λz) if data allow. Plasma levels of CAB will be measured during the Follow-up phase between weeks 41 to 89 to determine λz and t1/2 for the final injection interval starting at Week 33.

9.6. Pharmacodynamics

Blood draws are listed in the SoA and Section 9.5 to assess the relationship between drug levels and or the emergence of adverse events (HIV acquisition).

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

10.1.1. Hypotheses

No formal statistical hypotheses will be evaluated. The study is designed to evaluate the PK, safety, tolerability, and acceptability of the injectable agent, CAB LA (600 mg dose administered at 8-week intervals after 2 initial doses 4 weeks apart) in HIV-uninfected men in China where at least 60% of the men are of a population who have sex with men. Where appropriate, an estimation approach will be taken, and point estimates and confidence intervals will be constructed.

10.1.2. Sample Size Considerations

The sample size of 40 participants given the CAB LA treatment was chosen to ensure an adequate evaluation of safety, tolerability and pharmacokinetics data in this population prior to moving into a large phase 3 study.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Subjects Screened Population	The All Subjects Screened Population will include all subjects who consent to participate in the clinical study. Subjects in this population will be used for disposition summary
Safety Population	The Safety Population will include all subjects who receive at least one dose of the study treatment. Subjects in this population will be used for all demographic and safety summaries or listings.
Oral Pharmacokinetic (PK) Population	The Oral PK Population will include those subjects in the Safety population for whom at least one evaluable intensive Oral PK sample will be obtained and analyzed. Oral pharmacokinetic samples that may be affected by protocol deviations will be reviewed by the study team and determined whether the or not the sample will be excluded. All Oral PK analyses will be based on this analysis population.
Injection Pharmacokinetic (PK) Population	The Injection PK Population will include all subjects in the Safety population for whom at least one evaluable Injection PK sample will be obtained and analyzed. Injection pharmacokinetic samples that may be affected by protocol deviations will be reviewed by the study team and determined whether or not the sample will be excluded. All Injection PK analyses will be based on this analysis population.

10.3. Statistical Analyses

The primary safety analysis and PK analyses including both oral phase and injection phase through Weeks 5 to 41 will be performed after all ongoing participants complete the Week 41 visit and datasets have been authorized. Other secondary analyses as mentioned, where appropriate, will also be performed. The end of study analysis will be performed after all ongoing participants complete the Week 89 visit.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by participant, study period or phase, visit, actual study day, and time if applicable. Summary tables and figures will be presented by visit and time if applicable.

The baseline or pre-dose assessment is the last available assessment prior to the time of the first dose unless it is specified otherwise. If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables or as noted in the Reporting and Analysis Plan (RAP).

Complete details of the planned analysis will be documented in the RAP.

10.3.1. Primary Analyses

10.3.1.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

The primary safety analysis will include Grade 2 or higher clinical and laboratory events that occur from the initial injection to 8 weeks after the last injection among participants who receive at least one injection. In an extended safety analysis, all data from enrolled participants will be analyzed regardless of how many injections they receive.

To assess safety, the number and the percentage of participants experiencing each safety endpoint will be tabulated. Each participant will contribute once in each category (i.e., only for the highest severity AE for each participant) for the calculation of event rates.

10.3.1.1.1. Injection Site Reaction (ISR)

The number and percentage of participants experiencing each type of injection site reaction sign or symptom will be tabulated by severity. For a given sign or symptom, each participant's ISR will be counted once under the maximum severity for all injection visits.

10.3.1.1.2. AEs

AEs will be tabulated using MedDRA preferred terms. The number and percentage of participants experiencing each specific AEs (All AEs, Grade 2 or higher, and SAEs) will be tabulated by severity and by relationship to study product. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity or the strongest relationship to study product. AEs leading to withdrawal will also be summarized. AEs will be summarized for those that are treatment emergent during LA dosing separately from those that are treatment emergent during oral dosing and also for those that are treatment emergent across the entire treatment phase of the study (combining both LA and oral dosing).

10.3.1.2. Pharmacokinetic Analysis

Plasma PK parameters will be generated in accordance to Section 9.5.

Concentration-time data summaries should include number (n), mean, standard deviation (SD), coefficient of variation (%CV), geometric mean, geometric mean coefficient of variation (% CVb), 95% CI, median, minimum, and maximum. Concentration-time data will be summarized using all data for each planned visit regardless of timing as well as for evaluable data that falls within allowable windows for each visit (to be defined in the RAP). Unless stated otherwise, descriptive summaries will include number (n), mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum for continuous variables, n and percent (%) for categorical variables, and geometric mean, 95% confidence interval (CI), and the between-participant CV (% CV_b) for the log_e-transformed PK parameters.

Accumulation of plasma CAB following CAB LA will be determined by using point estimates and confidence intervals for difference in least squares means for the following comparison:

Comparison	Test	Reference
Accumulation	1 week post injection concentrations Week 34	1 week post injection concentrations Week 6

Time to steady state will be assessed by comparing plasma concentration of CAB at Week 41 (Cτ following 5th injection) to previous Cτ concentrations at Weeks 17, 25, and 33. This may be accomplished by visual inspection of graphical data or by calculating the point estimate and confidence interval for the slope for log(Cτ) by week for Weeks 25 through 41.

10.3.2. Secondary Analyses

Acceptability

To assess acceptability of the CAB LA, the proportion (with 95% CI) of participants who would consider using CAB LA for HIV prevention in the future will be calculated among all enrolled participants (including those who terminated product use during the trial). Participants will be asked if they would consider using CAB LA for HIV prevention in the future at their Week 41 visit or at their withdrawal visit, whichever occurs first.

Tolerability

To assess tolerability of CAB LA, the proportion of participants who terminate from receiving injections prior to the full course due to AE, intolerability of injection, frequency of injections, or burden of procedures related to injections out of those participants that received at least one injection.

A questionnaire will also be used to assess participant tolerability and satisfaction to the treatment. For each question the responses will be summarized by the proportion of participants reporting the response out of all those that answered the question. An overall treatment satisfaction score will be calculated for each participant.

10.3.3. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between CAB PK parameters and demography (age, weight, gender, race, and ethnicity) or pharmacodynamic (PD) (e.g., safety parameter) may be explored.

10.3.4. Pharmacogenetics

Pharmacogenetic analysis will not be conducted in this study.

10.3.5. Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the reporting and analysis plan. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

10.3.6. Interim Analyses

No interim analysis is planned for this study.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
AUC(0-τ)	Area under the plasma concentration time curve over the dosing interval t
BMI	Body mass index
BUN	Blood urea nitrogen
CAB	Cabotegravir
CAB LA	Cabotegravir long-acting
CDC	US Centers for Disease Control and Prevention
CI	Confidence interval
CL	Systemic clearance of parent drug
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
CPK	Creatine phosphokinase
CRF	Case Report Form
CV	Coefficient of variance
%CV	Percent coefficient of variation
%CVb	between-participant CV
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDIs	Drug-Drug Interactions
DILI	Drug Induced Liver Injury
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
FTC	Emtricitabine
GFR	Glomerular Filtration Rate
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice
GLS	Geometric Least-Squares
GSK	GlaxoSmithKline
GSK1265744	Cabotegravir (Both oral and LA formulations)
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus

HCV	Hepatitis C Virus
HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
HIV-PrevTSQc	HIV-Prevention Treatment Satisfaction Questionnaire change
HSR	Hypersensitivity Reactions
h/hr	Hour(s)
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
IC_{90} or IC90	90% of the maximum inhibitory concentration
ICF	Informed consent form
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug
INI	Integrase inhibitor
INR	International normalized ratio
INSTI	Integrase strand transfer inhibitor
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection site reactions
LA	Long acting
LDH	Lactate dehydrogenase
LFT	Liver Function Test
λz	Terminal phase rate constant
µg	Microgram
µL	Microliter
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
MSM	Men who have sex with men
n	Number
NAAT	Nucleic Acid Amplification Testing
OL	Open Label
PD	Pharmacodynamic
PGx	Pharmacogenetics
PI	Prediction interval
PK	Pharmacokinetic
PEP	Post exposure prophylaxis
POC	Point of care
PrEP	Pre-exposure prophylaxis
PTT	Partial thromboplastin time

Q4W	Every 4 weeks
Q8W	Every 8 weeks
RAP	Reporting and Analysis Plan
RNA	Ribose nucleic acid
RPV	Rilpivirine
SAE	Serious adverse event(s)
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SHIV	Simian/Human Immunodeficiency Virus
SIV	Simian Immunodeficiency Virus
SRM	Study Reference Manual
STI	Sexually transmitted infection
SOA	Schedule of Activity
t½	Terminal phase half-life
τ	Dosing interval
TDF	Tenofovir disproxilfumarate
tmax	Time of occurrence of Cmax
UGT	Uridine diphosphosphate-glucuronosyltransferase
ULN	Upper limit of normal
UK	United Kingdom
US	United States
USP	United States Pharmacopeia
ViiV	ViiV Healthcare
Vss	Volume of distribution at steady state
WHO	World Health Organization

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by ViiV Healthcare
MedDRA
Phoenix
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit WBC Count (absolute) Reticulocyte Count	RBC Indices: MCV MCH % Reticulocytes MCHC	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1,2]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose non fasting except for day 1 and week 41	Calcium	Alkaline phosphatase	Creatine phosphokinase (CPK)
	Total CO_2	Gamma glutamyltransferase (GGT)	Calculated creatinine clearance – Cockcroft-Gault equation	Uric Acid

Laboratory Assessments	**Parameters**			
	Albumin	Chloride	Glomerular Filtration Rate (GFR)	phosphate
	Lactate Dehydrogenase (LDH)			
Lipid Panel[2]	Total Cholesterol	High-density lipoprotein (HDL)	Low Density Lipoprotein (LDL)	Triglyceride
Coagulation Panel	Prothrombin Time (PT)	PTT	International normalized ratio (INR)	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) by dipstick • Microscopic examination (if blood or protein is abnormal)			
Urine Chemistry	• Microalbumin • Creatinine • Microalbumin/creatinine ratio			
Other Screening Tests	• HIV POC test; if positive will be confirmed by western blot, HIV ½ Multispot or the Geenius HIV Confirmation ½ Assay, and HIV RNA. • Hepatitis B surface antigen [HBsAg] and antibody[HBsAb], Hepatitis C (HCV) • Syphilis, Urine screening for Chlamydia, Gonorrhea screen. A positive TRUST for syphilis screen will reflex to a treponemal confirmation test. • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).			

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Test will be performed in the fasting state.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- 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

Informed Consent Process

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

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

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

Data Protection

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

Committees Structure

Not applicable

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.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- 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 after study completion 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.

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 Data Quality Plan.

Study and Site Closure

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

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

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

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

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

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

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 treatment 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 treatment 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.

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.

Cardiovascular Events (CV) Definition:

- 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

AEs of Special Interest:

Diarrhea

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

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

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

Hypertriglyceridemia/ Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the SoA table (Section 2). Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive IP. Clinical management of participants with hypertriglyceridemia/hypercholesterolemia should not be based upon non-fasting samples (obtained in the fed state). A confirmatory fasting triglyceride and/or cholesterol level should be obtained prior to the institution of medical therapy for hyperlipidemia. Isolated Grade 3 and Grade 4 lipid abnormalities do not require withdrawal of IP.

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

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, and concurrent conditions) should be taken into account, and a nephrology consult may be obtained.

Proximal Renal Tubule Dysfunctions

Proximal Renal Tubule Dysfunctions (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. other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained.

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.

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:
a. Results in death
b. 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.
c. 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 fulfils 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.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. 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.

Recording AE and SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently 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 treatment 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 treatment 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.

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.

- 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 by telephone.
- Contacts for SAE reporting can be found in the study reference manual.

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.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the study reference manual.

References

Dube MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, Tashima KT et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; 37(5):613-27.

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.

12.5. Appendix 5: Schedule for Additional Laboratory Procedures for Enrolled Participants who have a Reactive Positive HIV Test Result (Post-HIV Confirmation Visit)

Post-HIV Confirmation Visit	
Refer for care	X
Offer condoms and lubricant	X
HIV counseling	X
Clinical Evaluation and Procedures	
Blood collection for plasma storage[1]	X
Schedule follow up visits[2]	X
CD4 cell count	X
HIV viral load	X
HIV resistance testing	X

(1) Stored plasma samples will be collected from participants who acquire HIV infection, these assessments may include PK assessment, CD4, resistance testing, HIV subtyping, characterization of the virus and/or the host response to infection. These assessments will be performed retrospectively; results will not be returned to study sites or participants.
(2) Participants will continue to be followed every 12 weeks (Section 8.1.3)

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

Phase 1 Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology (in alignment with FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• A blood sample for pharmacokinetic (PK) analysis will be obtained at every visit, and therefore, should be available to match with Liver Function Test (LFT) findings. An additional PK sample should be obtained at the same time as any unscheduled LFT assessment.
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity e.g., fatigue, decreased appetite, nausea, vomiting, abdominal</td></tr>
</table>

Liver Chemistry Stopping Criteria	
recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	pain, jaundice, fever, or rash, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3xULN and bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

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

12.7. Appendix 7: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017

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.

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 +5mmHg 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	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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 (page 23 in source DAIDS Table).

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

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

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

[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	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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 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)
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 indicatedP	Life-threatening consequences

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

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

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

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

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

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

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

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

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

[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 (page 23 in source DAIDS Table).

[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*

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 in Source DAIDS TAble. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS TAble. Total Bilirubin for Term and Preterm Neonates
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*

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

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*

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

*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

[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

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

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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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_9} *to* *< 0.600 x* 10^9	350 to < 500 *0350 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*
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*

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

[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 femaile 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

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

Appendix A: Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], **High** (mg/dL; *µmol/L*)[19] ***Term Neonate***[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 μmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

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 (accessed 26 May 2017).

12.8. Appendix 8: Toxicity Management

ANEMIA

Grade 1 (mild) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 1 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin (abnormal if increased >50% from baseline)
3. haptoglobin (abnormal if ≤ 25 mg/dL)
4. reticulocyte count (abnormal if ≥ 4%)

If the additional tests are within the normal range, participants may continue study medication. If one or more of the additional tests is abnormal or suggestive of hemolytic anemia as specified above, participants will permanently discontinue study medication and be withdrawn from the trial. Participants should be followed up until resolution of anemia.

Grade 2 (moderate) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 2 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin (abnormal if increased > 50% from baseline)
3. haptoglobin (abnormal if ≤ 25 mg/dL)
4. reticulocyte count (abnormal if ≥ 4%)

If the additional tests are within the normal range, participants may continue study medication. If one or more of the additional tests is abnormal or suggestive of hemolytic anemia as specified above, participants will permanently discontinue study medication and be withdrawn from the trial. Consultation with a Hematologist should be considered. Participants should be followed up until resolution of anemia.

Grade 3 (severe) or Grade 4 (potentially life threatening) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 3 or 4 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin
3. haptoglobin
4. reticulocyte count

Participants will permanently discontinue study medication and be withdrawn from the trial. Consultation with a Hematologist should be considered. Participants should be followed up until resolution of anemia.

TOTAL BILIRUBIN ELEVATION

Grade 1 (mild) bilirubin elevation (1.1 - 1.5 times ULN) or Grade 2 (moderate - 1.6-2.5 times ULN):

Any bilirubin value above the upper limit of normal must be repeated and fractionated (direct and indirect bilirubin). Participants may continue study medication. Participants should be followed up until resolution (return to baseline) of elevation.

Grade 3 (severe – 2.6-5.0 times ULN) or 4 (life-threatening - > 5.0 times ULN) bilirubin elevation:

Any bilirubin value above the upper limit of normal must be repeated and fractionated (direct and indirect bilirubin). Participants will permanently discontinue study medication and be withdrawn from the trial. Participants should be followed up until resolution (return to baseline) of bilirubin elevation.

AST AND ALT ELEVATION

See Section 12.6.

RASH

Grade 1 rash (Localized macular rash):

Participants with Grade 1 rash should be evaluated by the Investigator immediately. A dermatologist may be consulted and a biopsy may be obtained if recommended by the dermatologist. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature >38.5°C
2. Lymphadenopathy
3. Pharyngitis
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 1 rash may continue the study drug at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 2.

Grade 2 rash (Diffuse macular, maculopapular, or morbilliform rash OR Target lesions):

Participants with Grade 2 rash should be evaluated by the Investigator immediately. Digital photographs should be obtained. A dermatologist may be consulted and a biopsy may be obtained if recommended by the dermatologist. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

- Temperature > 38.5°C
- Lymphadenopathy
- Pharyngitis
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 2 rash may continue the study drug at the discretion of the Investigator. It should be noted that oral mucosal **erosions** may be part of a Grade 2 rash. Any mucosal **ulceration** increases the severity of the rash to at least Grade 3. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 2.

Grade 3 rash (Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site):

Participants with a Grade 3 rash will permanently discontinue the study medication. The participant should be evaluated in the physician's office immediately and should be seen in the physician's office or contacted by phone every 2 days until the rash resolves. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed at the discretion of the Investigator. 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. The participant should remain on the study to be followed for safety and PK as outlined in Section 2.

Grade 4 rash (Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN):

Participants with a Grade 4 rash will permanently discontinue the study medication. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Sponsor and PPD Medical Monitor should be notified of this serious adverse event within 24hr via phone or fax. The participant should be closely followed everyday until resolution of the reaction. The participant should remain on the study to be followed for safety and PK as outlined in Section 2.

ALLERGIC REACTION

Grade 1 allergic reaction (Pruritis without rash):

Participants with Grade 1 allergic reaction should be evaluated by the Investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 1 allergic reaction may continue the study drug at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 2.

Grade 2 allergic reaction (Localized urticaria):

Participants with Grade 2 allergic reaction should be evaluated by the Investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 2 allergic reaction may continue the study drug at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 2.

Grade 3 allergic reaction (Generalized urticaria or angioedema):

Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Grade 4 allergic reaction (Anaphylaxis):

Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Revised ACTG Toxicity Grade	**Definitions**	**Investigator Action**
Grade 1	Pruritus without rash	May continue therapy
Grade 2	Localized urticaria	May continue therapy
Grade 3	Generalized urticaria Angioedema	Discontinue Therapy
Grade 4	Anaphylaxis	Discontinue Therapy

12.9. Appendix 9: HIV Testing Algorithm and Management of HIV Infection in Study Participants

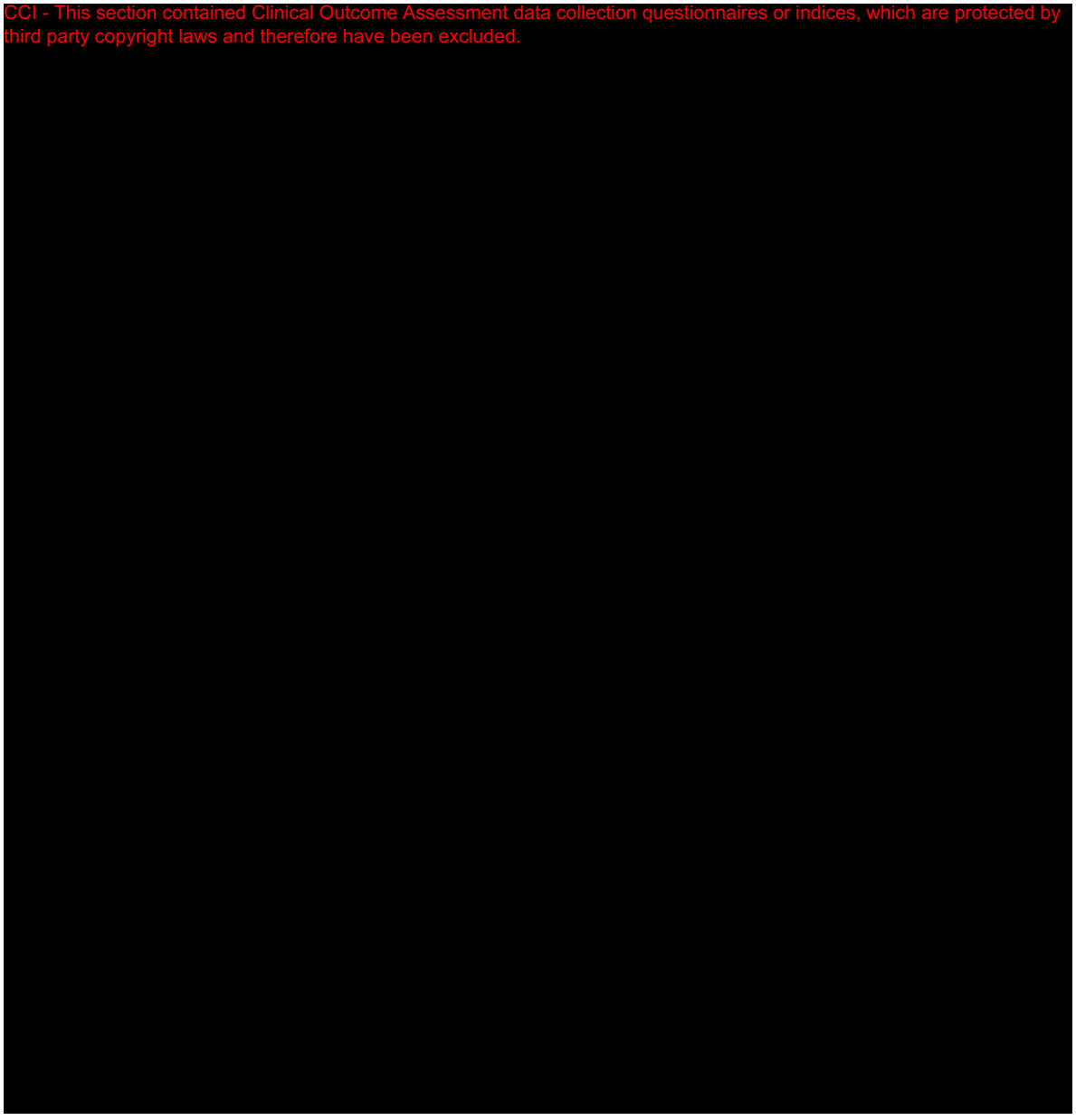
- HIV testing at Day 1 and the subsequent visits will use POC HIV testing kits in accordance with local standard operating procedures. Additional testing is required for participants who have a reactive or positive HIV test after enrolment. Stored plasma from the visit previous to the positive test should be tested for HIV using the 4th generation HIV test to best estimate time of infection. HIV acquisition must be confirmed by either western blot, HIV ½ Multispot or the Geenius HIV Confirmation ½ Assay, and HIV RNA (Branson, 2014).

Reference:

Branson BM., Owen SM., Wesolowski LG et al. CDC Reference Guide: Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. June 27, 2014.

12.10. Appendix 10: HIV-Prevention Treatment Satisfaction Questionnaire (change): (HIV-PrevTSQc)

For the past 10 weeks you have been taking part in a study of treatment to prevent HIV. The study began with 4 weeks of tablet treatment followed by five CAB LA 600 mg IM injections administered at 8-week intervals, with the first 2 doses given 4 weeks. Today we would like to know how your experience of your current prevention treatment with **injections** compares with your experience of prevention treatment with **tablets** during the first 4 weeks of the study. Please answer each question by circling a number on each of the scales. If you have experienced no change in your satisfaction with treatment, please circle '0'.



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.

Please make sure that you have circled one number on each of the scales.

Thank you for taking the time to complete this questionnaire.

12.11. Appendix 11: Daily Diary Card for Symptoms at Injection Area

GENERAL INSTRUCTIONS

An injection is another word for "shot" or "jab" and is how you have been receiving your study medication. This diary card will help us understand any symptoms you may have in the area where you receive the injections.

How to complete this Diary Card

- Make all the entries in black ink with a ball point pen.
- Print neatly so that your answers can be read easily.
- Complete dates as Day Month Year. Example: 15 October 2013 write 15 OCT 13.
- If you make a mistake, draw a single line through it.
-

Additional Instructions

- Complete the Diary Card every day.
- Some sections have a number scale. Use these scales to help you describe your symptoms.
- Please call the study site if you develop any symptoms which interfere with normal everyday activities, any temperature >38.3C, or any symptoms which cause you concern.

HOW TO DESCRIBE YOUR SYMPTOMS

Symptoms may appear around the area where you receive the injections. On the day you get the injections and for each day after, check the area where the injection was given for any itching, pain or any other symptoms. If you have any symptoms, complete **ALL** of the columns for that day. If you do not have any symptoms for that day, tick ( ) NO under the Symptoms column. Leave the remaining columns blank for that day.

Pain:

- Using the scale of 0-3, tick ( ) the number in the box that best describes the worst pain you feel around the area you received the injection.
  - 0 = No pain or tenderness
  - 1 = Pain or tenderness that is easily tolerated and does not interfere with your normal, everyday activities
  - 2 = Pain or tenderness that interferes with your normal, everyday activities
  - 3 = Pain or tenderness that prevents your normal, everyday activities

Itching:

- Using the scale of 0-3, tick ( ) the number in the box that best describes the worst itching around the injection area you felt that day.
  - 0 = No itching
  - 1 = Itching at the injection area that is easily tolerated and does not interfere with your normal, everyday activities
  - 2 = Itching at and around the injection area that interferes with your normal, everyday activities
  - 3 = Itching in a large area around the injection area that prevents your normal, everyday activities

Other Symptoms:

- Using a mirror and your hand, check for any bruising, skin firmness, discoloration, or bump in the area where you received the injection.
- Tick ( ) NO if you do not see or feel any of these other symptoms, or the appropriate word abbreviation for the symptoms that you do see or feel.

NO = None
BR = Bruising
BU = Bump
D = Discoloration
R = Redness
SF = Skin firmness
SW = Swelling
W = Warm to touch

<u>Home Treatment</u>:

- Please tick ( ) the appropriate word abbreviation. If you used or applied any treatment for your symptoms at the area of the injection at home, on your own, or with family/caregiver assistance.

NO = None
AP = Acetaminophen/paracetamol
D = Diphenhydramine
T = Topical anti-itch cream or ointment such as hydrocortisone/ diphenhydramine/TCM pain patch, etc.

W = Warm compress (heating pad)
C = Cold compress (cold pack or ice pack)
I = Ibuprofen

Exercise Habits:

For the week following your injection, please record your exercise habits.

- Tick ( ) YES if you performed any cardiovascular activity this week, then tick all activities you performed and record the total duration of your cardiovascular activities for the entire week (in minutes). Tick ( ) NO if you did not perform any cardiovascular activities this week.
- Tick ( ) YES if you performed any strength training exercise this week, then record the total duration of your strength training exercise for the entire week (in minutes). Tick ( ) NO if you did not perform any strength training exercises this week.
- Tick ( ) YES if you performed any other strenuous activity this week, then record the total duration for the entire week (in minutes) of your other strenuous activity. Tick ( ) NO if you did not perform any other strenuous activity this week.

Protocol Identifier	Subject Identifier	DAILY DIARY CARD FOR	Visit Description
206898		**INJECTION AREA SYMPTOMS**	( )Week 5 ( )Week 9 ( )Week 17 ( )Week 25 ( )Week 33

Day	Date	Symptoms ?		Pain (0 - 3)				Itching (0 - 3)				Other Symptoms								Home Treatment					
				0= No pain or tenderness Pain or tenderness that is 1= easily tolerated and does not interfere with your normal, everyday activities 2= Pain or tenderness that interferes with your normal, everyday activities 3= Pain or tenderness that prevents your normal, everyday activities				0 = No itching 1 = Itching at the injection area that is easily tolerated and does not interfere with your normal, everyday activities 2 = Itching at and around the injection area that interferes with your normal, everyday activities 3 = Itching in a large area that prevents your normal, everyday activities				NO = None BR = Bruising BU = Bump D = Discoloration R = Redness SF = Skin firmness SW = Swelling W = Warm to touch								NO = None AP = Acetaminophen/paracetamol I= Ibuprofen D = Diphenhydramine (Benadryl) Top = Topical anti-itch cream or ointment such as hydrocortisone/ diphenhydramine, TCM painpatch etc. W = Warm compress (heating pad) C = Cold compress (cold pack or ice pack)					
	DD/MMM/YY	Yes	No	0	1	2	3	0	1	2	3	NO	BR	BU	D	R	SF	SW	W	NO	AP/I	D	Top	W	C
e.g	*15 OCT 13*																								
First Day																									
Second Day																									
Third Day																									
Fourth Day																									

Fifth Day																									
Sixth Day																									
Seventh Day																									

If you have ongoing symptoms when you turn in this diary card, please continue to record the symptoms on the next diary card the study staff gives to you, until you no longer have the symptom.

Did you perform any cardiovascular activity this week?									Total Weekly Duration	**Did you perform any strength training exercise this week?**		Total Weekly Duration	**Did you perform any other strenuous activity this week?**		Total Weekly Duration
Yes	No	Run	Walk	Bike	Swim	Aerobic	Elliptical-Stairs	Other	(minutes)	Yes	No	(minutes)	Yes	No	(minutes)
									20						***20***

12.12. Appendix 12: Protocol Amendment History

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