TITLE PAGE

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Title:	A Phase 1, Multicompartmental Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N213747_00	2015-MAY-04	Original
2014N213747_01	2015-NOV-10	Amendment No. 1
Amendment 1 includes additional exclusion criteria for subjects with history of seizure disorder		
2014N213747_02	2016-MAR-30	Amendment No. 2
Amendment 2 updated the CAB LA IM dose from 800 mg (split 2 x 400 mg injections) to a single 600 mg IM dose. In addition, tissue collection on Day 3 (48h post-injection) was changed from optional assessments to required assessments per protocol and removed vaginal tissue collection on Day 8, Week 4 and 12. Lastly, MRI assessments were changed from optional assessments to required, updated dose rationale, and miscellaneous changes for clarification.		
2014N213747_03	2017-AUG-14	Amendment No. 3
Amendment 3 updated the wash-out period between oral and LA dosing to accommodate visit scheduling, and removed the needle length specification for intramuscular injection in Section 6.1.3.		

SPONSOR SIGNATORY

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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201767, Amendment 3

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201767

Rationale

Cabotegravir (CAB) long-acting (LA) is a promising candidate for HIV pre-exposure prophylaxis (PrEP) due to its potent antiretroviral activity and infrequent dosing requirements. Currently, the CAB concentrations achieved in the anatomical sites associated with sexual HIV transmission following the proposed 600 mg intramuscular PrEP dose are unknown. This Phase 1 study will provide a compartmental pharmacokinetic (PK) analysis of CAB following a single 600 mg intramuscular dose in healthy volunteers. These data will further our understanding of CAB distribution to the anatomical mucosal tissue believed to be relevant to sexual HIV-1 transmission and supplement the data available to support future PrEP clinical trial development. The study will include a 4 week oral dose lead-in to assess safety and tolerability, a 14-42 day washout period, and a single 600 mg dose of CAB LA administered as a single 3 mL intragluteal injection. Post-injection PK sampling will include blood plasma, vaginal, cervical and rectal tissue, as well as cervicovaginal and rectal fluid over 12 weeks.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To determine the pharmacokinetic concentrations of CAB following LA administration in blood plasma and in vaginal tissue (VT), cervical tissue (CT), and cervicovaginal fluid (CVF) in healthy women and in rectal tissue (RT) and rectal fluid (RF) in healthy men and women (as data permit) following a single 600 mg intramuscular dose.	• Concentrations observed at Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) in blood plasma and in CT, and CVF in women, and in RT and RF in men and women (as data permit) following a single CAB 600 mg intramuscular dose. • VT concentrations observed at Day 3 (C48h), and Week 8 (CWk8), in women following a single CAB 600 mg intramuscular dose.
Secondary	
• To compare the pharmacokinetic concentrations following a single intramuscular dose of CAB LA 600 mg in VT, CT, and CVF relative to blood plasma and CVF in healthy women, and in RT and RF relative to blood plasma and RF in healthy men and women (as data permit).	• Concentration ratios including VT:blood plasma, CT:blood plasma, CVF:blood plasma, CT:CVF, VT:CVF in women, and RT:blood plasma, RF:blood plasma and RT:RF in men and women (as data permit) at matched timepoints evaluated.
• To describe the pharmacokinetic profile of CAB LA in blood plasma and CT, CVF, in healthy women and in RT and RF in healthy men and women (as data permit) following a single 600 mg intramuscular dose.	• Maximum observed concentration (Cmax) and time of maximum observed concentration (tmax) in blood plasma and in CT, CVF, RT, RF matrices. • Area under the concentration time curve from time zero to last quantifiable time point (AUC(0-last)), area under the concentration time curve from time zero to infinity (AUC(0-∞)), area under the concentration time curve from time zero to Week 4 (AUC(0-Wk4)), area under the

Objectives	Endpoints
	concentration time curve from time zero to Week 8 (AUC(0-Wk8)) area under the concentration time curve from time zero to Week 12 (AUC(0-Wk12)) and apparent terminal phase half-life ($t_{½}$) in blood plasma, CT, CVF, RT, RF, as data permit. • Tissue:blood plasma and fluid:blood plasma ratio of AUCs of intervals specified above.
• To determine the trough concentration achieved following repeat administration of oral CAB 30 mg once daily to steady state in blood plasma and VT, CT, and CVF in healthy women and in RT and RF in healthy men and women (as data permit).	• CAB concentration (C_{24}) following oral administration in VT, CT, CVF, RT, RF and blood plasma.
• To assess the safety and tolerability of CAB following repeat oral doses and single dose intramuscular administration in healthy subjects.	• Safety and tolerability parameters, including adverse events, clinical laboratory tests, and vital signs assessments.
Exploratory	
• To assess evolution of the injection depot localization following a single CAB 600 mg intramuscular dose.	• Volumetric and T1,T2 assessment of depot via non-contrast-enhanced MRI images of the injection site at the time of injection, Day 3 (48 hours), and 1 week post-injection as data permit.

Overall Design

This will be a Phase 1, open label study in healthy subjects to assess the pharmacokinetics of CAB LA in the blood plasma and anatomic locations associated with sexual HIV-1 transmission: vaginal tissue (VT), cervical tissue (CT), cervicovaginal fluid (CVF), rectal tissue (RT), and rectal fluid (RF). The study will consist of a screening period, a 28-day oral lead-in phase using a CAB dose of 30 mg once per day followed by a 14-42 day washout period, and a single dose of CAB LA 600 mg IM with compartmental PK sampling for up to 12 weeks. Subjects will return for safety assessments and PK sampling of the blood plasma at Week 24 and Week 36 post-injection and undergo a follow-up visit at Week 52 post-injection or withdrawal visit if a subject is terminated earlier.

Study Design*

Screening	Oral Lead-in	Washout	CAB Injection and Compartmental PK Sampling	Safety/ Blood Plasma Sampling	Follow-up/ Withdrawal Visit
Within 30 days of 1st oral CAB dose	Oral CAB 30 mg tablet once daily x 4 weeks	No drug administered 14 –42 days	Single 600 mg CAB LA IM dose Tissue/luminal fluid/blood plasma sampling up to 12 weeks post-injection	Safety assessments and blood plasma PK sampling will occur at 24 and 36 Weeks post-dose	Follow-up assessments to be performed 52 Weeks post-injection

*Given the cervicovaginal sampling in the protocol, timing and duration of menses should be taken into account when scheduling screening, oral lead-in phase and injection.

Treatment Arms and Duration

Each subject will participate in the study for approximately up to 66 weeks. All subjects will undergo screening assessments within 30 days of the oral-lead in phase. If eligible to participate, subjects will proceed to the oral lead-in phase during which they will self-administer CAB 30 mg orally once daily for 28 days and undergo PK sampling on Day 29. All subjects will have a 14 – 42 day washout period where no CAB will be administered. After the washout period, each subject will receive a single ultrasound-guided 600 mg (1 x 3 mL injection) IM dose of CAB LA into gluteal muscle and undergo PK sampling for up to 12 weeks. After the Week 12 assessments, subjects will return to the clinic for safety assessments and additional blood plasma PK sampling at 24, 36, and 52 weeks post CAB injection.

Type and Number of Subjects

Approximately 20 healthy subjects from up to two clinic sites will be enrolled such that approximately 16 evaluable subjects (8 males and 8 females) will receive a CAB LA IM dose and complete compartmental PK sampling. Non-contrast-enhanced magnetic resonance imaging (MRI) will be performed in a subset of up to 4 males and 4 females.

Analysis

Samples of plasma, tissues, and secretions will be assayed for CAB concentrations using HPLC-MS/MS. Pharmacokinetic parameters will be estimated via noncompartmental analysis using WinNonlin program (Version 5.2 or higher, Pharsight, Inc., Cary, NC).

All the derived PK parameters will be listed and summarized by gender and overall. For each of these PK parameters, with the exception of tmax and ratios, the following descriptive summary statistics will be calculated for each treatment: n, arithmetic mean with associated 95% CI, standard deviation, median, minimum, maximum, geometric mean with associated 95% CI, standard deviation of logarithmically transformed data, and between-subject coefficient of variation (CVb(%)). For tmax and ratios, no geometric mean, nor associated 95% CI or standard deviation of logarithmically transformed data will be provided.

2. INTRODUCTION

CAB is an investigational HIV-1 integrase strand transfer inhibitor (INSTI) currently being developed as both an oral tablet and nanosuspension formulation suitable for a long-acting (LA) intramuscular (IM) injection. The development of CAB is based on its potential for a high genetic barrier to resistance and a pharmacokinetic (PK) profile allowing for low-dose, once-daily oral administration or monthly to quarterly IM dosing using a nanosuspension formulation. These attributes have led to the development of the compound for both the treatment of HIV-1 infection, as well as pre-exposure prophylaxis (PrEP) indications.

2.1. Study Rationale

This Phase 1 study aims to describe the PK profile of CAB LA in blood plasma, vaginal tissue (VT), cervical tissue (CT), cervicovaginal fluid (CVF), rectal tissue (RT), and rectal mucosal fluid (RF) following a single 600 mg intramuscular dose. A compartmental PK analysis of CAB will further our understanding of CAB distribution to the anatomical sites believed to be relevant to sexual HIV-1 transmission. Previously, CAB concentrations have been determined in CT, VT, and RT for up to 12 weeks following a single 400 mg intramuscular dose [Table 1, GlaxoSmithKline Document Number 2013N159605_00]. Tissue: plasma ratios were low: 16-28% in cervicovaginal tissue and ≤8% in rectal tissue (Table 2). Assuming a tissue density of 1g/mL, median cervical and vaginal tissue concentrations were approximately equivalent to the *in vitro* protein adjusted (PA)-IC_{90} (0.166µg/mL) at some visits. As a linear relationship between tissue and plasma concentrations was observed graphically, tissue concentrations are predicted to increase at higher doses of CAB LA which produce plasma concentrations in the target therapeutic range. This study will extend our understanding of CAB LA as a preventative agent and determine the concentrations achieved in the anatomical sites associated with sexual HIV-1 transmission following a single 600 mg IM LA dose. These data can be utilized to build complex pharmacometric, multi-compartment models that may significantly inform clinical trial simulations and study design in the future.

Table 1 Summary of CAB LA Tissue Concentrations by Visit (LAI114433)[1]

Tissue Type	Tissue Concentration (µg/g) (n=4/visit)			
	400 mg IM unsplit (Cohort 8)		400 mg IM split (2x 200 mg IM, Cohort 9)	
	Week 2	Week 8	Week 4	Week 12
Cervical	0.081 (NQ- 0.17)	0.096 (0.06 - 0.19)	0.177 (0.07- 0.50)	0.133 (NQ - 0.21)[3]
Vaginal[2]	0.121 (NQ - 0.18)	0.184 (0.09 - 0.44)	0.155 (NQ - 0.90)	0.181 (NQ - 0.35)
Rectal[2]	NQ (NQ - 0.10)	NQ (NQ - 0.05)	0.079 (NQ - 0.20)	0.063 (NQ - 0.08)

Data source: LAI114433 Clinical Pharmacology Study Report

1. median (range)
2. n=8 samples
3. n=3 samples

NQ- Non-quantifiable concentration measured as below LLQ

Table 2 Summary of Overall CAB LA Tissue:Plasma Ratios by Tissue Type (LAI114433)[1]

	400 mg IM unsplit (Cohort 8)	400 mg IM split (2x 200 mg IM, Cohort 9)
Cervical[2]	0.20 (0.0 - 0.40)	0.16 (0.0 - 0.4)
Vaginal[3]	0.28 (0.0 - 0.7)	0.19 (0.0 - 0.7)
Rectal[3]	0.00 (0.0 - 0.1)	0.08 (0.0 - 0.2)

Data source: LAI114433 Clinical Pharmacology Study Report

1. median (range) (across all visits and subjects)
2. n=8 unsplit; n=7 split
3. n=24

2.2. Brief Background

CAB is an investigational HIV-1 INSTI that possesses attributes favorable for both HIV treatment and prevention indications. CAB has demonstrated potent *in vitro* activity against a broad range of HIV strains. Due to its unique physiochemical properties, CAB has been formulated as both a once daily oral tablet and a LA nanosuspension for monthly to quarterly intramuscular administration. The CAB tablet will serve as oral lead-in therapy to assess safety and tolerability prior to switching to the LA formulation for HIV-1 treatment and/or prevention. The LA-injectable, which has a plasma half-life of approximately 21-50 days, is a promising candidate for PrEP and has demonstrated protective antiviral activity in both rectal and vaginal non-human primate (NHP) Simian/Human Immunodeficiency Virus (SHIV)-challenge models [Andrews, 2014; Radzio, 2015].

In a preclinical study, eight male rhesus macaques were injected with CAB LA (50 mg/kg IM) at two time points, 1 week prior to the first virus exposure and 4 weeks later [Andrews, 2014]. An additional eight male macaques were untreated and served as placebo controls. After weekly intrarectal challenges with SHIV162p3 [50 tissue culture infective dose $(TCID)_{50}$] for up to eight exposures, all eight placebo macaques became infected after a median of two rectal exposures (range 1 to 7). Of the eight CAB LA-treated macaques, none had detectable systemic viremia 10 weeks after the last virus challenge. In these protected animals, the plasma concentrations of CAB throughout the period of virus challenges were comparable to clinically relevant exposure in humans. In a similarly designed study, three intramuscular doses of CAB 50 mg/kg administered 4 weeks apart fully protected female pigtail macaques (n=6) from twice weekly low dose (50 $TCID_{50}$) SHIV162p3 challenges [Radzio, 2015]. These data support the continued development of CAB LA as a PrEP candidate for both men and women at high risk for HIV transmission.

As of 01 January 2016, approximately 1160 adult subjects have been exposed to CAB in either oral or injectable formulations. Both healthy volunteers and HIV-infected patients have been dosed with oral CAB, and approximately 566 healthy volunteers and HIV-infected patients have received at least 1 injection of CAB LA. Previous Phase I and on-going Phase II studies have demonstrated that CAB is well tolerated when administered as both a once daily oral tablet and LA IM injection. The safety, tolerability, and

acceptability of CAB LA in HIV uninfected men is currently being evaluated in the ECLAIR study [GlaxoSmithKline Document Number 2013N184048_01] and will be assessed in HIV uninfected men and women in the HPTN 077 Phase 2 study.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To determine the pharmacokinetic concentrations of CAB following LA administration in blood plasma and in vaginal tissue (VT), cervical tissue (CT), and cervicovaginal fluid (CVF) in healthy women and in rectal tissue (RT) and rectal fluid (RF) in healthy men and women (as data permit) following a single 600 mg intramuscular dose.	• Concentrations observed at Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) in blood plasma and in CT, and CVF in women, and in RT and RF in men and women (as data permit) following a single CAB 600 mg intramuscular dose. • VT concentrations observed at Day 3 (C48h), and Week 8 (CWk8), in women following a single CAB 600 mg intramuscular dose.
Secondary	
• To compare the pharmacokinetic concentrations following a single intramuscular dose of CAB LA 600 mg in VT, CT, and CVF relative to blood plasma and CVF in healthy women, and in RT and RF relative to blood plasma and RF in healthy men and women (as data permit) .	• Concentration ratios including VT:blood plasma, CT:blood plasma, CVF:blood plasma, CT:CVF, VT:CVF in women, and RT:blood plasma, RF:blood plasma and RT:RF in men and women (as data permit) at matched timepoints evaluated.
• To describe the pharmacokinetic profile of CAB LA in blood plasma and CT, CVF, in healthy women and in RT and RF in healthy men and women (as data permit) following a single 600 mg intramuscular dose.	• Maximum observed concentration (Cmax) and time of maximum observed concentration (tmax) in blood plasma and in CT, CVF, RT, RF matrices. • Area under the concentration time curve from time zero to last quantifiable time point (AUC(0-last)), area under the concentration time curve from time zero to infinity (AUC(0-∞)), area under the concentration time curve from time zero to Week 4 (AUC(0-Wk4)), area under the concentration time curve from time zero to Week 8 (AUC(0-Wk8)), area under the concentration time curve from time zero to Week 12 (AUC(0-Wk12)) and apparent terminal phase half-life (t½) in blood plasma, CT, CVF, RT, RF, as data permit.. • Tissue:blood plasma and fluid:blood plasma ratio of AUCs of intervals specified above..

Objectives	Endpoints
• To determine the trough concentration achieved following repeat administration of oral CAB 30 mg once daily to steady state in blood plasma and VT, CT, and CVF in healthy women and in RT and RF in healthy men and women (as data permit).	• CAB concentration (C_{24}) following oral administration in VT, CT, CVF, RT, RF and blood plasma
• To assess the safety and tolerability of CAB following repeat oral doses and single dose intramuscular administration in healthy subjects.	• Safety and tolerability parameters, including adverse events, clinical laboratory tests, and vital signs assessments
Exploratory	
• To assess evolution of the injection depot localization following a single CAB 600 mg intramuscular dose.	• Volumetric and T1, T2 assessment of depot via non-contrast-enhanced MRI images of the injection site at the time of injection, Day 3 (48 hours), and 1 week post-injection as data permit.

4. STUDY DESIGN

4.1. Overall Design

This will be a Phase 1, open label study in healthy subjects to assess the PK of CAB LA in blood plasma and anatomical tissues and secretions associated with sexual HIV-1 transmission following a single 600 mg IM dose. The study will consist of a screening period, a 28-day oral lead-in phase at a CAB dose of 30 mg once per day followed by a 14-42 day washout period, and a single dose of CAB LA 600 mg with compartmental PK sampling for up to 12 weeks. Subjects will return for safety assessments and PK sampling of the blood plasma at Week 24 and Week 36 post-injection and undergo a follow-up visit at Week 52 post-injection or a withdrawal visit if a subject is terminated earlier.

Table 3 Study Design*

Screening	Oral Lead-in	Washout	CAB Injection and Compartmental PK Sampling	Safety/ Blood Plasma Sampling	Follow-up/ Withdrawal Visit
Within 30 days of 1st oral CAB dose	Oral CAB 30 mg tablet once daily x 4 weeks	No drug administered 14 – 42 days	Single 600 mg CAB LA IM dose Tissue/luminal fluid/blood plasma sampling up to 12 weeks post-injection	Safety assessments and blood plasma PK sampling will occur at 24 and 36 Weeks post-dose	Follow-up assessments to be performed 52 Weeks post-injection

*Given the cervicovaginal sampling in the protocol, timing and duration of menses should be taken into account when scheduling screening, oral lead-in phase and injection.

4.1.1. Screening

All subjects will undergo a screening visit within 30 days of the first dose of the oral-lead in. Subjects may be rescreened once. Subjects who are enrolled into the trial and

subsequently withdrawn from the study, for any reason, may not be re-screened. Subjects may continue to the oral lead-in phase as soon as all eligibility requirements have been met.

4.1.2. Oral Lead-in Phase

Subjects that are eligible to participate will return to the clinic on Day 1 of the oral lead-in phase and receive their first oral dose of CAB 30 mg after the completion of all pre-dose assessments as outlined in the Time and Events Table (Section 7.1). Subjects will be dispensed a sufficient supply of oral CAB 30 mg tablets to complete 27 days of once daily dosing at home and be counseled to take their dose at about the same time each day. On Day 14 of the oral lead-in phase, subjects will return to the clinic to assess safety, tolerability, and subject adherence to study drug. Subjects should bring their supply of oral CAB to the Day 14 visit to have drug accountability performed.

Subjects will return to the clinic on Day 29 to have drug accountability, PK and all assessments performed as described in the Time and Events Table (Section 7.1). Subjects will undergo PK sampling of blood plasma and CT/VT/CVF (females) and/or RT/RF. Female subjects who consent to rectal tissue and rectal fluid sampling will have paired rectal and genital tract samples collected at each timepoint. Female subjects who do not wish to participate in rectal PK sampling may still participate in the study. Every attempt should be made to acquire PK samples approximately 24 hours after the last outpatient dose of CAB 30 mg. After receiving their last dose of oral CAB 30 mg on Day 28, subjects will begin a 14-42 day wash-out period, during which no CAB will be administered.

4.1.3. CAB Injection and PK Sampling

After a minimum of a 14-day washout period, subjects will return to the clinic and receive a single dose of CAB LA 600 mg IM into the gluteal muscle. To ensure that injections are given IM rather than subcutaneously, ultrasound guidance during injection will be used. Subjects will remain in the research unit for at least 4 hours after the injection for PK sampling and safety assessments. Non-contrast-enhanced MRI imaging will be performed as outlined in the Time and Events Table (Section 7.1) in a subset of approximately 8 subjects (4 females and 4 males) to assess evolution of the injection depot localization. Subjects will return to the research unit for PK sampling and for study assessments as described in the Time and Events Table (Section 7.1).

Subjects who receive an injection of CAB LA will return to the clinic for safety assessments and plasma PK sampling at Week 24 and Week 36 post-injection, as well as the follow-up/withdrawal visit as outlined in Section 4.1.4.

4.1.4. Follow-up/Withdrawal Visit

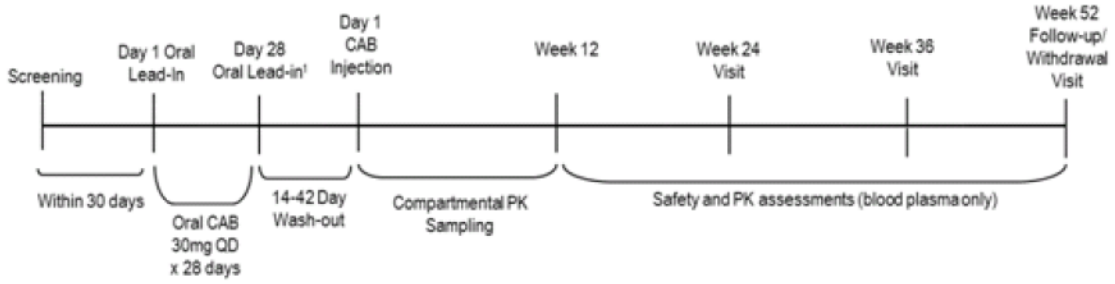
Because of the long acting pharmacokinetic profile of CAB LA, every effort should be made to bring subjects back in through the 52 weeks following the CAB LA injection. A final follow-up visit will be planned for Week 52 post-injection. If a subject is withdrawn prior to receiving the CAB LA injection, then a follow-up/withdrawal visit should be scheduled 10-14 days after the last oral dose of CAB. If a subject is withdrawn

or disqualified from the study after receiving the CAB LA injection, because of the long acting pharmacokinetic profile of CAB LA every effort should be made to bring the subject back in for the 52 weeks of safety and PK assessments following the injection. Further detail regarding withdrawal/follow-up procedures can be found in Section 5.4.

4.2. Treatment Arms and Duration

Each subject will participate in the study for approximately up to 66 weeks.

Figure 1 Study Schematic



1. In addition to compartmental PK sampling following CAB LA injection, subjects will undergo PK sampling of blood plasma and CT/VT/CVF (females) and/or RT/RF after Day 28 of the oral lead-in, on Day 29.

4.3. Type and Number of Subjects

Approximately 20 healthy subjects from at least two clinic sites will be enrolled such that approximately 16 evaluable subjects (8 males and 8 females) will receive a CAB LA IM injection and complete 12 weeks of PK sampling. Non-contrast-enhanced MRI imaging will be performed in a subset of up to 8 subjects (4 males and 4 females). Evaluable subjects are defined as those who provide at least one primary PK endpoint without major protocol deviations.

If subjects prematurely discontinue the study or is not-evaluable, additional replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator. The replacement subject will have same treatment and procedures per protocol as the discontinued subject.

4.4. Design Justification

The rectal and vaginal mucosa are likely relevant sites of CAB action when used to prevent sexual HIV transmission. After IM injection of 400 mg of CAB LA in earlier PK studies, tissue to plasma ratios were low, at 16-28% for cervicovaginal tissue and <8% for colorectal tissue [Spreen, 2014]. The aim of this study is to determine the multi-site PK of CAB LA IM for 12 weeks following a 600 mg IM dose.

Because the current planned CAB LA injection dose frequency is every 8 weeks, we plan PK sampling of blood plasma, cervicovaginal and rectal luminal fluid, and biopsies of cervical, vaginal, and rectal tissue at the end of the 4 week oral lead-in and at 1 week, 4 weeks, 8 weeks, and 12 weeks post-injection to understand drug exposure at all of these

sites throughout a dosing interval and as concentrations wane through Week 12 post-injection. An additional luminal fluid (CVF and/or RF) and tissue (CT/VT and/or RT) sample will be collected on Day 3 (approximately 48 hours post-injection) to assess the early distribution of CAB into the genital tract and rectal compartments. In addition to the paired blood plasma samples, blood plasma will be collected at additional timepoints through the extended safety visits for approximately one year after injection as outlined in Section 7.1. This sampling scheme will provide a comprehensive assessment of CAB LA PK following a single 600 mg IM dose (Table 4).

Table 4 Compartmental PK Sampling

	Compartmental PK Sampling Times	
Sex	**Oral Lead-In**	**Post 600 mg IM Dose**
Females (BP/VT/CT/CVF/RT[1]/RF[1])	**Day 29** Rectal fluid and rectal tissue is optional[1]	**Day 3 (48h), Day 8 (168h), Week 4, Week 8, Week 12** Rectal fluid and Rectal tissue optional at each timepoint[1]; Vaginal tissue will be collected only on Day 3 (48h) and Week 8.
Males (BP/RT/RF)	**Day 29**	**Day 3 (48h), Day 8 (168h), Week 4, Week 8, Week 12**

1. Female subjects will be given the choice to provide near simultaneous paired rectal compartment samples at each fluid and tissue sampling time-point. This is an optional assessment for which women must provide consent. Female subjects who do not wish to participate in rectal PK sampling may still participate in the study.

Female subjects will be given the choice to provide near simultaneous paired rectal compartment samples at each fluid and tissue sampling timepoint. Consent must be obtained prior to collecting rectal tissue or rectal fluid samples from female participants. Rectal PK samples are optional for female subjects and, therefore, females who do not wish to participate in rectal PK sampling may still participate in the study. Tissue and fluid concentrations obtained from paired rectal and genital tract samples will enhance our understanding of anatomic variation in CAB distribution and allow between-gender comparisons in rectal compartment penetration.

To improve the consistency of IM dosing, we will administer the CAB LA injection with ultrasound guidance. Post-injection magnetic resonance imaging (MRI) will also be performed in a subset of subjects to assess the changes over time in the injection depot volume.

In order to maximize subject safety, a 4 week oral CAB lead-in phase will precede the injection to identify those subjects with adverse drug reactions prior to the CAB LA injection. If a Grade 3 or above AE is observed, or any AE that is deemed clinically significant by the investigator and is judged by the investigator to be attributed to the study product or procedures, the subject will be withdrawn and will not receive the CAB injection. If the subject is withdrawn prior to injection, a follow up visit will be performed 10-14 days after the last oral dose of study drug.

This design is well-established for the evaluation of multi-compartmental pharmacokinetics. It is subject to Institutional Review Board (IRB) approval and the appropriate regulatory approvals, and will be listed on the website ClinicalTrials.gov. No blinding or placebo control will be used, as these are not necessary for the purposes of this study.

4.5. Dose Justification

Oral Dose:

Based upon the results through Week 48 of the Phase IIb, LAI116482 study, and in accordance with the pre-specified dose selection criteria at Week 24, CAB 30 mg PO once daily has been selected as part of short-term oral lead-in therapy in combination with rilpivirine for maintenance of virologic suppression in future clinical studies in subjects with HIV infection as well as for short-term oral lead-in therapy as CAB monotherapy prior to CAB LA injectable dosing in the ÉCLAIR and HPTN077 PrEP studies in healthy uninfected subjects [GlaxoSmithKline Document Number 2013N184048_01; DAIDS Document ID 11964, 2014]. Therefore, the CAB 30 mg oral dose will be administered during the oral lead-in phase of this study to assess safety and tolerability prior to the CAB IM injection.

LA Dose:

In an early study, a small cohort of healthy participants receiving two quarterly doses (Q12W) of CAB LA 800 mg IM achieved a geometric mean (CVb%) $C\tau$ of 1.11 mg/mL (139%), approximately 6.7-fold above the PA-IC_{90} and between the 5 mg and 10 mg oral doses. These data, as well other PK data following CAB LA following single or repeat doses ranging from 100 mg to 800 mg IM, were included in the initial population PK model. Based on the initial population PK model, CAB LA 800 mg IM given every 12 weeks (Q12W) was predicted to achieve a mean concentration above the 1.35 µg/mL target based on 10 mg daily oral dosing with the lower bound of the 90% confidence interval (CI) at ~4-fold PA IC_{90}. The overall range of predicted CAB $C\tau$ values following CAB LA 800 mg IM was similar to that following once daily dosing of oral CAB 10 mg.

The Phase 2a 201120 (ÉCLAIR) study was undertaken to evaluate PK and safety following Q12W CAB LA 800 mg IM doses in healthy male participants. Evaluation of PK data from ÉCLAIR showed that 30 to 37% of CAB LA $C\tau$ values were ≥4-fold PA-IC_{90} following each of the three quarterly injections while 15 to 31% were below the PA-IC_{90}. Graphical evaluation of the CAB plasma concentration-time profiles suggests that absorption was more rapid among participants in the ÉCLAIR study than that observed in prior studies, resulting in higher peak and lower trough concentrations. Of note, the CAB LA nanosuspension formulation has remained essentially unchanged throughout the clinical development program, indicating that other factors are contributing to the observed PK differences. Given this information, a regimen of CAB LA 800 mg Q12W may not maintain sufficient exposures in all participants, particularly in males. The ongoing Phase 2a study 201103 (HPTN 077), which like ÉCLAIR is evaluating CAB LA 800 mg IM Q12W in healthy male and female participants, was amended to enroll a

second cohort with dosing of CAB LA 600 mg IM at two time points 4 weeks apart and every 8 weeks (Q8W) thereafter for 5 injection visits. A similar regimen (CAB LA 800 mg IM initial dose followed by 600 mg IM at two time points 4 weeks apart and Q8W thereafter) has been evaluated in HIV infected participants (n=115; 107 males and 8 females) in combination with rilpivirine (RPV) LA in study 200056 (LATTE-2). This regimen achieved a mean CAB Cτ of 1.53µg/mL (median 1.45µg/mL) at Week 32, above the geometric mean Cτ value for the 10 mg oral dose in LATTE. At Week 32, the proportion of participants maintaining suppression of HIV in the Q8W arm was 95% as compared to 94% in the Q4W arm (CAB LA 800 mg IM initial dose followed by 400 mg IM every 4 weeks from Week 4, n=115).

The CAB population PK model has been updated with PK data from ÉCLAIR (an additional 94 males) and LATTE-2 (an additional 230 participants; 216 males and 14 females), significantly increasing the data in the population PK dataset. The absorption rate constant for the entire population following CAB LA for the new model was increased approximately 2-fold (4.54 x 10-4 hr-1 to 9.19 x 10-4 hr-1; i.e., more rapid absorption) as compared to the previous model and resulted in higher peak to trough ratios than previously observed. Sex remains a significant covariate in the model affecting the absorption rate constant following LA administration (KA LA), reflecting slower absorption in females than in males. Additional data from HPTN077 will increase the data obtained from females in the model to improve understanding of the impact of sex on KA LA.

Simulations based on the updated population PK model have been conducted to evaluate several potential dosing regimens. Currently, the HPTN077 Cohort 2 regimen (CAB LA 600 mg IM at two time points 4 weeks apart and every 8 weeks (Q8W) thereafter) is planned for evaluation in long-term Phase 3 PrEP studies. CAB LA 600 mg IM is the largest CAB LA dose that can be administered by single injection (3mL of 200 mg/mL nanosuspension). For these reasons, a single 600 mg IM is the proposed dose for evaluation of plasma and tissue PK in this study. Simulated profiles following a single CAB LA 600 mg IM injection one week after discontinuation of the CAB 30 mg once daily oral lead-in to evaluate safety are shown for males and females separately (Figure 2, Figure 3). The profiles show the last oral dose, which are expected to achieve mean peak and trough concentrations of 7.5µg/mL and 4.2µg/mL, respectively. Consistent with the impact of sex on absorption, males will achieve a higher Cmax of ~3µg/mL than females, who will achieve a Cmax of ~1.35µg/mL. Plasma concentrations are expected to remain above 4x PA-IC_{90} (0.664µg/mL) for approximately 4 weeks and above PA-IC_{90} (0.166µg/mL) for approximately 8 weeks in 95% of males; greater variability in concentrations between 8 and 12 weeks post injection is expected in males. Plasma concentrations are expected to remain above the PA-IC_{90} (0.166µg/mL) in 95% of females throughout the 12-week tissue sampling period.

Figure 2 **Predicted Median (90% PI) CAB Concentration-time Profile in Males following a single CAB LA 600 mg IM Injection (after a 1 week washout from 30 mg once daily oral lead-in)**

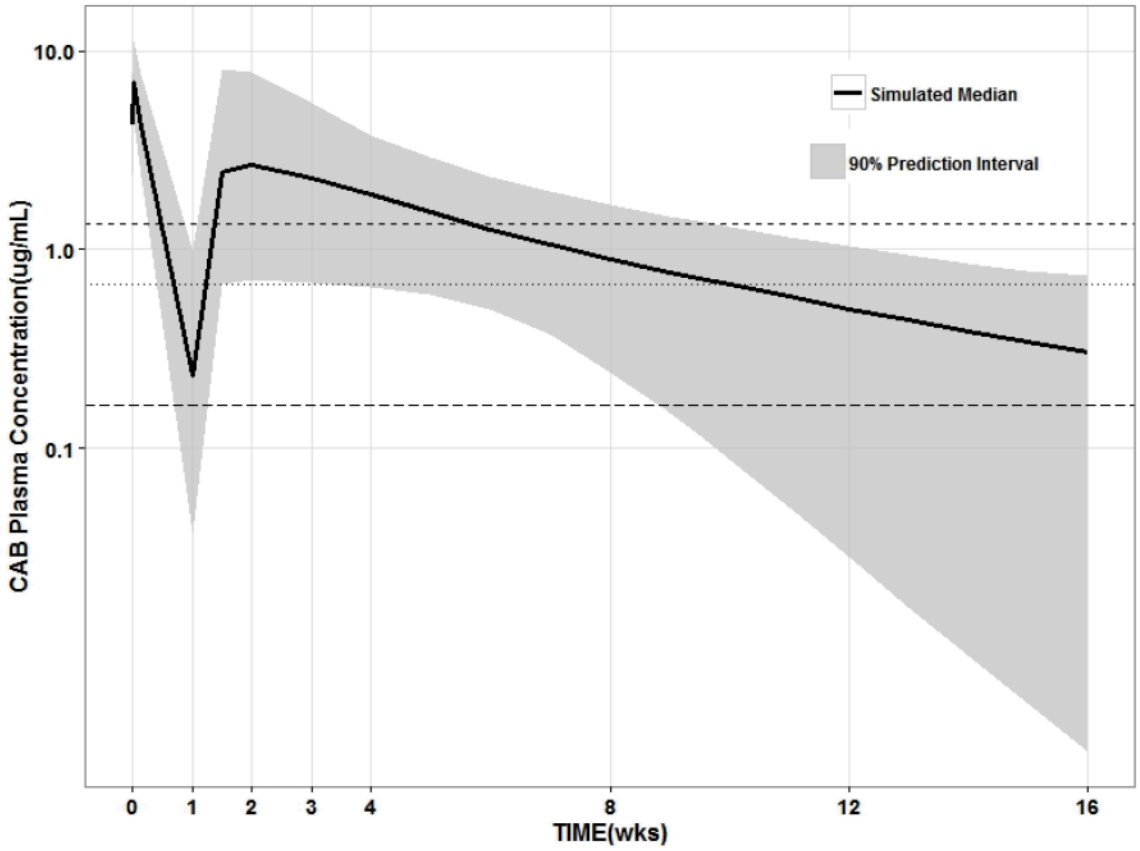
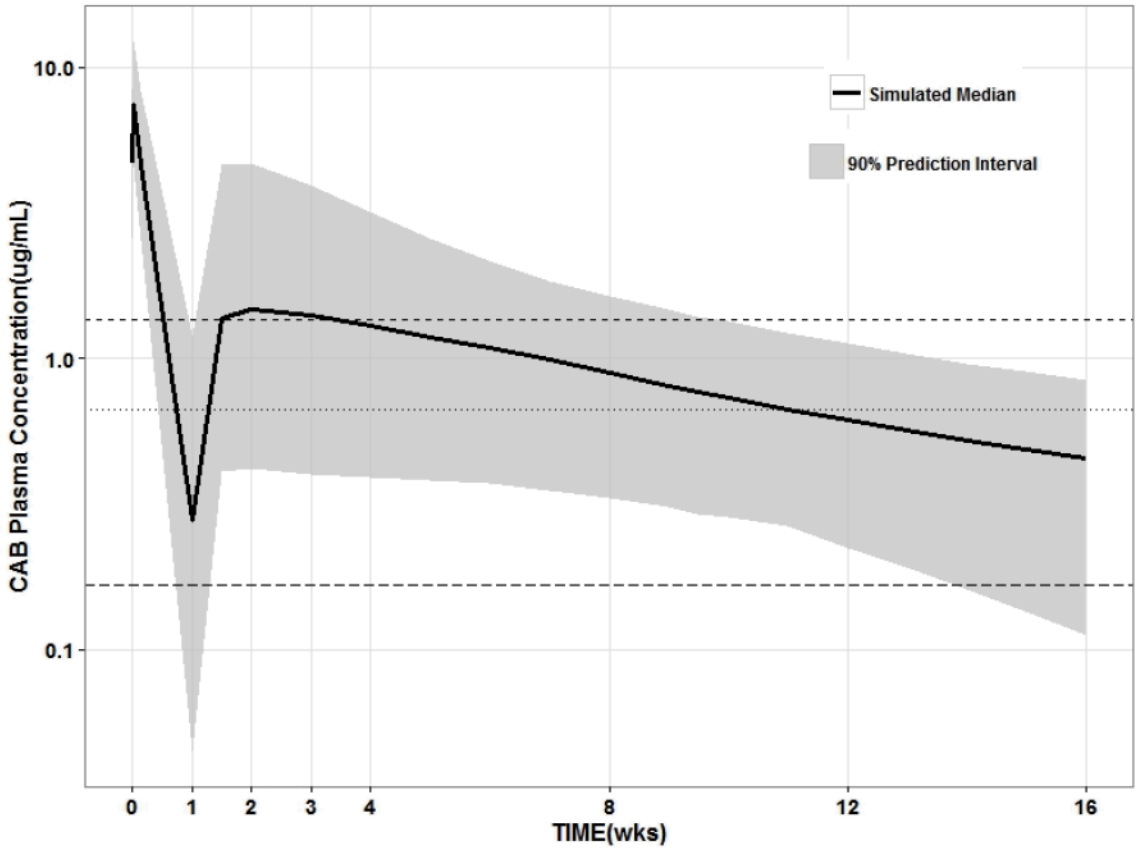


Figure 3 Predicted Median (90% PI) CAB Concentration-time Profile in Females following a single CAB LA 600 mg IM Injection (after a 1 week washout from 30 mg once daily oral lead-in)



In a previous study, a modest correlation between plasma CAB concentrations and cervicovaginal and rectal tissue concentrations was observed following a single dose of CAB LA 400 mg IM in healthy male and female subjects (Section 2.1). As the proposed dose is 50% higher and tissue sampling will be conducted during the oral phase and following CAB LA administration, it is expected that tissue sampling will be conducted over an ~100-fold range of plasma concentrations (~ 0.05µg/mL to ~5µg/mL). The partitioning of CAB into genital tract and rectal tissue achieved over a 12-week window following a single CAB LA 600 mg IM dose will enhance our understanding of CAB LA as PrEP.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with CAB can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK1265744/Cabotegravir		
Elevated liver transaminases	A few subjects in the CAB program have experienced transaminitis (elevated liver transaminases characterised by predominant ALT elevation). Some of these subjects' transient transaminitis were explained by acute hepatitis C infection and others did not have alternative explanations, suggesting a mild form of Drug induced Liver Injurt (DILI) without hepatic dysfunction which resolved upon withdrawal of treatment with CAB. Cumulatively (through January 1, 2016) 1160 subjects have been exposed to oral CAB and/or IM CAB. Seventeen subjects have met protocol-defined liver stopping criteria, of which five are considered to represent possible or probable cases of DILI. Eight of the 17 subjects met liver stopping criteria after having received CAB IM, six subjects as a result of acute Hepatitis C, one acute HIV seroconversion and one possible or probable DILI following CAB IM or Placebo IM administration. Of the five subjects with possible or probable cases of DILI, four subjects were receiving oral CAB and one subject developed probable DILI following CAB IM or Placebo IM administration. None of these subjects have developed evidence of hepatic dysfunction and all had improvements in AST and ALT over time upon withdrawal of CAB.	Exclusion criteria as described in Section 5.2 will prohibit subjects with current or chronic liver diseases and significant liver impairment based on screening liver chemistry including transaminases (ALT and AST). A 4-week oral lead- in period is being implemented in this study, where all subjects will receive oral CAB prior to the administration of IM CAB to determine individual safety and tolerability Liver transaminases (ALT and AST) will be closely monitored throughout this study (refer to Time & Events Table) and the liver chemistry stopping criteria will be adopted as described in Section 5.4.1 of this protocol. Subjects will be withdrawn from CAB treatment where no compelling alternative cause is identified All instances of liver transaminase elevations will be followed to resolution. Subjects withdrawn from CAB treatment due to meeting liver chemistry stopping criteria will be regularly monitored both clinically and using liver chemistries to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		determine progress towards resolution of the liver event
Injection Site Reactions (ISRs)	Clinical, experience to date has demonstrated ISRs occur in the majority of exposed subjects treated with IM CAB 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 subject 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 subjects' withdrawal due to ISRs. None of the ISRs was serious and no clinical significant complications were reported	Administration advice to minimize risk of poor administration technique giving rise to ISRs. Advice on care, monitoring, natural course, and treatment of ISRs given in study documentation Advice to subjects on care of injection site on day/days immediately post administration, use of analgesia, compresses where appropriate. Subjects will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. Complications of ISRs such as infections (abscess, cellulitis) and collections of fluid requiring drainage will be monitored Significant ISRs may be photographed and referred to a dermatologist for specialist advice. .

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity Reactions (HSR)	Hypersensitivity reactions have been reported with integrase inhibitors, including 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 hypersensitivity reaction, were it to occur.	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 CAB to determine individual safety and tolerability prior to the introduction of IM CAB. Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this study (refer to Time & Events Table). Results from these assessments may aid early detection of HSR. Oral CAB will be withdrawn immediately for cases with suspected HSR during the lead-in phase. During oral and IM CAB treatment, any HSR reactions that occur would be managed supportively.
Drug-Drug Interactions (DDIs)	Residual concentrations of CAB will remain in the systemic circulation of subjects for prolonged periods (months). Subjects discontinuing a LA regimen may be at risk for developing DDIs many weeks after discontinuing injectable therapy. Of note, in vitro and clinical evidence to date, indicates that with the exception of sensitive OAT substrates with narrow therapeutic index (e.g. methotrexate), CAB has a low risk for causing clinically significant drug interactions.	All subjects will be informed of prohibited medications throughout the study and updates provided as needed via informed consent.
Development of Resistance in the setting of HIV acquisition	Residual concentrations of CAB LA would remain in the systemic circulation of participants for prolonged periods (up to 52 weeks in some subjects). Participants 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 informed of this risk. Participants will be followed for 52 weeks from the time of the last injection with CAB. The risk of HIV acquisition should be minimized by

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		only including healthy volunteers at low risk for acquiring HIV, and by encouraging all subjects to practice safe sex for at least 52 weeks after the last injection of CAB LA. HIV testing will occur periodically throughout the study. If a participant acquires HIV on study he or she will be referred for appropriate care.
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular injection, it is possible that IM CAB can be inadvertently administered intravenously instead of intramuscularly resulting in higher than expected concentrations of CAB. This could be due to administrator error, improper injection technique and / or improper needle length used based on body type. The clinical consequences of overdose with CAB are currently unknown.	All IM injections will be done under ultrasound guidance by a trained clinician, which will minimize the risk of intravenous administration. Should IM maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose ECG , vital signs or any other supportive testing may be obtained at the discretion of the investigator, and the medical monitor notified. Laboratory samples for safety parameters will be closely monitored in all subjects. Additionally, 2 hour post dose PK samples will be obtained at a few early timepoints for determination of CAB concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Anoscopy to obtain rectal fluid sampling	It is possible that the participant may experience mild discomfort, embarrassment or, rarely, pain (should they have another condition that is already causing pain in the area) during this procedure.	If there is any pain experienced during the procedures, the study clinician will adapt or stop the procedure.
Cervical and vaginal biopsy via speculum exam	It is possible that the participant may experience mild discomfort, embarrassment, or, rarely, pain during speculum exam and biopsies. There is also a small risk of bleeding and an extremely low risk of infection after biopsy. In rare circumstances, the bleeding may require blood transfusions and surgical repair. A small amount of discomfort during sexual intercourse may follow in the few days after the procedure.	If there is an adverse event, participants will be referred immediately to the appropriate care. If there is any pain experienced during the procedures, the study clinician will adapt or stop the procedures. Subjects should abstain from inserting anything into the vagina (e.g., tampons, sexual intercourse) within 72 hours after cervical or vaginal biopsies.
Colonic biopsies via flexible sigmoidoscopy	Flexible sigmoidoscopy is a commonly practiced medical procedure and the endoscopic procedures done in this trial will not involve any unusual risks or discomforts. The risks associated with these procedures include mild discomfort and the feeling of having a "bloated stomach". Endoscopic biopsies are painless and heal quickly within 3 days. On extremely rare occasions, the endoscopic procedure or biopsies may lead to pain, infection (sepsis), bleeding or perforation of the gastrointestinal tract. Perforation occurs approximately once out of every 10,000 procedures. If this extremely rare complication occurs, antibiotics and surgery to repair the tear may be necessary. In rare circumstances, the bleeding may require blood transfusions and surgical repair. Subjects will self-administer a 125 mL enema several hours prior to the flexible sigmoidoscopy procedure. The main risk from having an enema is temporary discomfort. Some air may be pumped into the rectum as well, causing a bloating or gassy sensation. Very rarely, the enema tip may cause a perforation, as described above. Subjects will also be asked to have nothing to eat for 8 hours prior to the endoscopy procedure.	This procedure will be performed exclusively by experienced practitioners of endoscopy, who are familiar with safety procedures and mitigation of any complications that should ensue.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Phlebotomy for blood draws	There is a small risk of discomfort, bleeding, inadvertent arterial puncture, or adverse reaction with venipuncture such as fainting.	Should any bleeding occur, the procedure will be aborted at that puncture site and pressure will be held for the appropriate period of time. Should any adverse reactions to venipuncture occur, the participant will be referred immediately to the appropriate care.
Other		
Ultrasound guidance for IM injection	There is no convincing evidence of adverse effects from ultrasound imaging, especially one-time, short-lived imaging which is expected to last less than a minute. No or minimal pain is associated with this procedure. According to the World Federation of Ultrasound in Medicine and Biology Clinical Safety Statement for Diagnostic Ultrasound Imaging (http://www.wfumb.org/about/statements.aspx), "Diagnostic ultrasound has been widely used in clinical medicine for many years with no proven deleterious effects. However, investigations into the possibility of subtle or transient effects are still at an early stage. Biological effects (such as localized pulmonary capillary bleeding) have been reported in mammalian systems at diagnostically relevant exposures but the clinical significance of such effects is not yet known. Consequently, diagnostic ultrasound can only be considered safe if used prudently. Ultrasound produces heating, pressure changes and mechanical disturbances in tissue. Diagnostic levels of ultrasound are capable of producing temperature rises that may be hazardous to sensitive organs and the embryo/fetus. Biological effects of non-thermal origin have been reported in animals but, to date, no such effects have been demonstrated in humans, except when a microbubble contrast agent is present.	Ultrasound will be employed for the minimum time necessary in order to obtain the required visualization and will be performed by competent personnel who are trained and updated in safe procedural technique
MRI (non-enhanced) of injection site to visualize injection depot	FDA guidance on safety and use of Magnetic Resonance Imaging (http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/ucm200086.htm) states: "MRI does not use ionizing radiation (high-energy radiation that can potentially cause damage to DNA, like the x-rays used CT scans). There are no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. However, there are important safety concerns to consider before performing or undergoing an MRI scan:	All participants will be screened according to local hospital criteria and trial inclusion/exclusion before entering the MRI room to ensure they are able to have the MRI conducted to maximize the safety of this procedure.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• The magnet may cause pacemakers, artificial limbs, and other implanted medical devices that contain metal to malfunction or heat up during the exam. • Any loose metal object may cause damage or injury if it gets pulled toward the magnet. • Dyes from tattoos or tattooed eyeliner can cause skin or eye irritation. • Medication patches can cause a skin burn. • The wire leads used to monitor an electrocardiogram (ECG) trace or respiration during a scan must be placed carefully to avoid causing a skin burn. Prolonged exposure to radio waves during the scan could lead to slight warming of the body."	

4.6.1.1. Other Clinically Relevant Information

Additional details concerning safety observations from clinical studies and for which a causal association has not been established or which are of minimal clinical significance may be found in the Investigator's Brochure. Please refer to Section 6: 'Summary of Data and Guidance for the Investigator'.

Adverse Events of Special Interest

Seizure
Three cases of seizures have occurred in the cabotegravir program cumulatively through 01 October 2015. 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 all studies. Subjects with recent history of, or recent treatment for seizure will be excluded from study participation.

4.6.2. Benefit Assessment

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

Benefit considerations may include:

- Contributing to the process of developing new therapies for HIV treatment and prevention that are not critically dependent upon adherence to daily dosing.
- Medical evaluations and assessments associated with study procedures (e.g. physical exam, ECG, laboratory studies, etc.).

4.6.3. Overall Benefit:Risk Conclusion

Review of the cumulative safety data on CAB oral and LA has not identified any safety signals which are considered to pose an unacceptable risk to healthy volunteers. Considering the multiple and overlapping measures that will be taken to minimize risk to subjects participating in this study, the potential risks identified in association with CAB are justified by the anticipated benefits that may be afforded to subjects including close medical monitoring and satisfaction of contributing to the ongoing continued clinical development of CAB for both the treatment and prevention of HIV infection.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

5.1. Inclusion Criteria

This study does not involve a randomization procedure, as all subjects will receive the same dose of the same product.

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the ViiV Healthcare investigational product or other study treatment that may impact subject eligibility is provided in the Investigator's Brochure.

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

AGE
1. Between 18 and 55 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. 3. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. A single repeat of a procedure or lab parameter is allowed to determine eligibility.

WEIGHT
4. Body weight $\geq$ 40 kg and body mass index (BMI) within the range 18.5 to 35 kg/m^2 (inclusive).

SEX
5. Male or female

6. A female subject is eligible to participate if she is pre-menopausal, has an intact uterus and cervix, AND is not pregnant (as confirmed by a negative human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Documented Bilateral Oophorectomy

b. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until at least five terminal half-lives OR until any continuing pharmacologic effect has ended, whichever is longer (can be up to 66 weeks on study) after the last dose of study medication and completion of the follow-up visit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
- Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]
- Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
- Injectable progestogen [Hatcher, 2007a]
- Percutaneous contraceptive patches [Hatcher, 2007a]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. Female subjects desiring pregnancy or foresee that they might wish to become pregnant within 52 weeks of receiving a CAB LA injection must be excluded.

All subjects participating in the study must be counseled on safe sexual practices including the use of effective barrier methods to minimize risk of HIV transmission.

INFORMED CONSENT
7. Capable of giving signed informed consent as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

Liver Function:

1. ALT or AST > ULN
2. Total bilirubin >ULN (isolated total bilirubin >ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

QTc Interval:

4. QTc > 450 msec

NOTES:

- The QTc is the QT interval corrected for heart rate according to Bazette's formula (QTc(QTcF B), machine-read or manually over-read.
- QTcB will be used to determine eligibility for an individual subject.
- For purposes of data analysis, QTcB or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).
- Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<45 and >100 bpm	<50 and >100 bpm
QRS duration	>120 msec	
QTc interval	>450 msec	

5. The subject's systolic blood pressure is outside the range of 90-140mmHg, or diastolic blood pressure is outside the range of 45–90mmHg.
6. History of clinically significant cardiovascular disease including:
   - Evidence of previous myocardial infarction (pathologic Q waves, S-T segment changes (except early repolarization).
   - History/evidence of symptomatic arrhythmia, angina/ischemia, coronary

artery bypass grafting (CABG) surgery or percutaneous transluminal coronary angioplasty (PCTA) or any clinically significant cardiac disease.

- Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree (type II) or higher], Wolf Parkinson White [WPW] syndrome).
- Sinus pauses > 3 seconds.

7. Any significant arrhythmia which, in the opinion of the principal Investigator and GSK Medical Monitor, will interfere with the safety for the individual subject. Non-sustained (≥3 consecutive ventricular ectopic beats) or sustained ventricular tachycardia.
8. History of ongoing or clinically relevant seizure disorder within the previous 2 years, including subjects who have required treatment for seizures within this time period. A prior history of seizure, with a seizure free period of at least 2 years, off anti-epileptics, may be considered for enrolment if the investigator believes the risk of seizure recurrence is low. All cases of prior seizure history should be discussed with the medical monitor prior to enrolment.

CONCOMITANT MEDICATIONS

9. The use of any concurrent prohibited medications as outlined in Section 6.10.2

RELEVANT HABITS

10. History of regular alcohol consumption within 6 months of the study defined as: An average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 ml) of beer, 5 ounces (150 ml) of wine or 1.5 ounces (45 ml) of 80 proof distilled spirits.
11. Inability or unwillingness to comply with lifestyle and/or dietary restrictions outlined in Section 6.9.
12. High-risk behavior for HIV infection which includes, but is not limited to one of the following risk factors within six months before entering the study (day 1 of the oral lead-in): Unprotected vaginal or anal sex with a known HIV-infected person or a casual partner, engaged in sex work for money or drugs, acquired a sexually transmitted disease, high risk partner currently or in the previous six months or intravenous drug use.

CONTRAINDICATIONS
13. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation. 14. For subjects participating in MRI imaging: Contraindication for MRI scanning (as assessed by local MRI safety questionnaire), which includes but is not limited to: a. Intracranial aneurysm clips (except Sugita) or other non-MRI compatible metallic objects b. Intra- orbital metal fragments that have not been removed by a medical professional c. Pacemakers or other implanted cardiac rhythm management devices and non-MRI compatible heart valves d. Inner ear implants e. History of claustrophobia

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
15. Positive hepatitis B surface antigen, or a positive hepatitis B core antibody with negative hepatitis B surface antibody) test result at screening or within 3 months prior to first dose of study treatment. 16. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment 17. A positive pre-study drug/alcohol screen (specific drugs are listed in Section 7.4.6). A positive drug screen is permitted if due to a prescribed medication, provided that medication is not on the list of prohibited medications in Section 6.10.2 and approved by the investigator and medical monitor. 18. A positive test for HIV antibody. 19. A positive pre-study screen for sexually transmitted diseases including *Neisseria gonorrhoea* or *Chlamydia trachomatis*, Trichomonas, syphilis, or an active HSV genital lesion. 20. Presence of a tattoo or other dermatological condition overlying the buttocks which in the opinion of the investigator may interfere with the interpretation of injection site reactions. 21. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 22. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
23. Where participation in the study would result in donation of blood or blood products in excess of 500 ml within a 56 day period. 24. Unwillingness or inability to follow the procedures outlined in the protocol. 25. Subject is mentally or legally incapacitated. **Additional Criteria for <u>Female</u> Subjects Only:** 26. Any current medical conditions that in the opinion of the investigator may compromise the conduct or analysis of the genital tract sampling (e.g., active genital tract infection or lesions). 27. Inability to abstain from the use of intravaginal products (e.g. tampons, spermicides, lubricants, vaginal hygiene products, diaphragms) for 72 hours prior to the genital tract sample collection visits and for up to 72 hours after. 28. Inability to abstain from any sexual activity (e.g., vaginal intercourse, masturbation, and penetration of the vagina by penises, fingers, tampons, sex toys) for 72 hours prior to the genital tract sample collection visits and for up to 72 hours after. **Additional Criteria for Male Subjects and Female Subjects who consent to rectal PK sampling:** 29. Any current medical conditions that in the opinion of the investigator may compromise the conduct or analysis of the rectal compartment sampling (e.g., active rectal compartment infection, lesions or disease). 30. Inability to abstain from the use of intrarectal products (e.g., suppositories, lubricants) for 72 hours prior to the rectal compartment sample collection visits and for up to 72 hours after. 31. Inability to abstain from any receptive anal sexual activity (e.g., anal receptive intercourse and penetration of the rectum by fingers, sex toys or other) for 72 hours prior to the rectal compartment sample collection visit and for up to 72 hours after.

5.3. Screening/Baseline/Run-in Failures

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

5.4. Withdrawal/Stopping Criteria

Subjects may voluntarily withdraw from the study at any time and for any reason. Site investigators and study staff may withdraw participants before their scheduled termination visit for safety, behavioral, or administrative reasons, or if the participants are unable or unwilling to comply with study procedures. The reasons for withdrawals will be recorded in the participants' study records. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

During the oral lead-in period, early withdrawal on medical grounds will occur if the participant develops a grade 3 or higher AE that is judged by the investigator to be related directly to the study product (see Appendix 3 and Appendix 4 for definitions and grading of severity of adverse events), or any AE that is deemed clinically significant by the investigator and is judged by the investigator to be related directly to the study product. For liver-related stopping criteria, please refer to Section 5.4.1.

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

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

- Pregnancy (please see Section 7.4.2)
- Protocol deviation
- Non-compliance
- Subject withdraws consent
- Subject lost to follow-up
- Investigator discretion
- Sponsor discontinues study

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

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

For participants who have only received oral doses of CAB and develop an adverse effect which meets criteria for stopping the administration of study product, safety visits and follow-up will be continued until the resolution of the event, and then the subject will be withdrawn from the study and will not receive the CAB LA injection. If participants are unable to receive the IM injection for any reason, they will have a follow-up/withdrawal visit within 10-14 days of the last oral dose of CAB and then be terminated from the study. If the reason is HIV acquisition or pregnancy, refer to Section 7.4.1.6 and Section 7.4.2, respectively. For participants who develop an adverse effect which meets criteria for stopping the administration of study product, and have received both the oral CAB and an IM injection of CAB LA, follow-up and safety visits will be continued for a total of 52 weeks after the injection of CAB LA. All follow-up visits and scheduled safety evaluations (enumerated in the Time and Events Table in Section 7.1) will remain the same.

The medical monitor should be informed of all study withdrawals.

5.4.1. Liver Chemistry Stopping Criteria

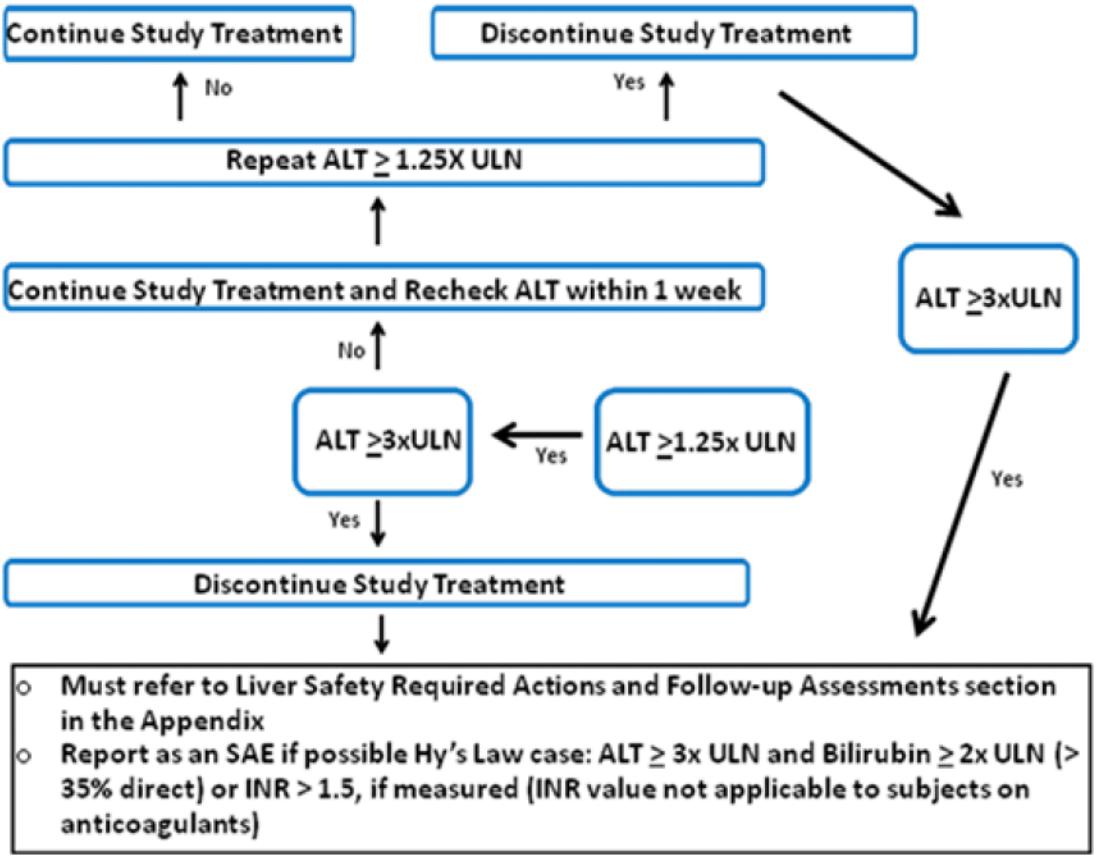
For subjects with ALT elevation ≥ 1.25x but < 3xULN, retest ALT within one week. If the retest ALT is < 1.25x ULN, subjects may continue to Day 28 dosing. If the retest ALT is ≥ 1.25x ULN, dosing will be terminated, and subjects are prohibited from entering the injection phase. Weekly assessments should be conducted until ALT is < 1.25x ULN. For subjects with ALT elevation ≥ 1.25x ULN at Day 29, dosing will be terminated, subjects are prohibited from entering the injection phase, and weekly assessments should be conducted until ALT is < 1.25x ULN. Subjects with ALT ≥ 3xULN at any time point will be discontinued from study treatment. Please refer to the Liver Safety Required Actions and Follow up Assessments Section in Appendix 2 for subsequent evaluations. If any of the above develops, please notify the medical monitor.

Standard liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the

FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a subject** if liver chemistry stopping criteria are met prior to CAB LA injection. If liver stopping criteria are met after receiving a CAB LA injection, subjects will not be withdrawn from the study but continue to have safety assessments performed as noted below and within the Time and Events table for 52 weeks post-injection or until resolution of the liver event, whichever is longer.

Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.2. QTc Stopping Criteria

- The same QTc correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled. For this protocol, the QTcB will be used for *all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording perio*d*. If the follow-up ECG shows a QTc that meets any of the stopping criteria listed below, three confirmatory ECGs should be done over a brief recording period (e.g., 5 – 10 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

A subject that meets the bulleted criterion *b*elow will be withdrawn from the study.

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

5.5. Subject and Study Completion

A subject that receives at least one dose of oral CAB, but withdraws early from treatment is considered a non-completer for treatment and study. Every effort should be made to bring the subject back in for a follow-up visit within 10 – 14 days of the last dose of study medication.

A subject that receives the CAB LA injection and completes the PK assessments for 12 weeks but withdraws prior to the 52 week follow up visit, will be considered completing the treatment phase of the study, but not a study completer.

A subject that withdraws after injection and does not complete PK assessments through week 12 is considered a non-completer for treatment and study. Because of the long acting pharmacokinetic profile of CAB LA every effort should be made to bring the subject back in for the 52 weeks of safety and PK assessments following the injection.

A completed subject is one who has completed all phases of the study including the 52 week follow up period. This subject will be considered a treatment and study completer.

The date of end of the study is defined as the last subject's last contact.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment	
Product name:	Oral CAB	CAB LA Injectable Suspension
Formulation description:	GSK1265744B, lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, magnesium stearate, Aquarius film-coating, white BP18237	Sterile Suspension for Injection
Dosage form:	Tablet	Vial
Unit dose strength(s)/Dosage level(s):	Dose level: 1 tablet Tablet strength: 30 mg	Each vial contains 400 mg/2 mL suspension of CAB
Route of Administration:	Administer orally, once daily	Intramuscular Injection
Dosing instructions:	Take 1 tablet orally every 24 hours	Gently invert suspension vial for 20 seconds to re-suspend sediment. Allow bubbles to subside, then use a syringe to withdraw the required volume of suspension for IM injection. Detailed instructions are provided in the study reference manual (SRM).
Physical description:	Tablets are white to almost white coated oval tablets	Sterile white to slightly pink suspension containing 400 mg/2mL of CAB for administration by intramuscular injection
Method for individualizing dosage:	One 30 mg tablet taken once a day for 4 weeks.	1 X 3 mL Injections (3 mL [600 mg] total) IM given once on Day 1 of injection phase.

6.1.1. Cabotegravir- Tablet

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

6.1.2. Cabotegravir- Injectable Suspension

The IP CAB LA is manufactured by GSK and is a sterile white to slightly pink suspension containing 200 mg/mL of CAB as free acid for administration by intramuscular injection. The product is packaged in a 3 mL USP Type I glass vial with a 13 mm gray stopper and aluminium seal. 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.

6.1.3. Dosing Considerations for CAB LA

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.

Sites may use their discretion as to where in the gluteus muscle the injection is given according to individual subject circumstance.

The protocol for injection will be as follows: The patient's buttock region will be imaged to identify the gluteal muscle, and a mark will be placed over a suitable area. After cleaning the skin with alcohol swab, under direct ultrasound visualization, a 22-gauge spinal needle will be introduced into the gluteal muscle. Then 600 mg CAB LA (concentration = 200 mg/mL (3 mL) will be injected as a single IM injection slowly under continuous ultrasound visualization. Pre- and post- injection images will be recorded onto the ultrasound Picture Archival and Communication System (PACS) system. The location (left/right) and time of injection will be captured in the eCRF.

Further dosing instructions can be found in the SRM.

6.2. Treatment Assignment

All eligible subjects will complete a 4-week CAB oral lead-in (30 mg oral tablet daily) period followed by a 14-42day washout period. On Day 1, all subjects will receive a single 600 mg IM dose of CAB LA.

6.3. Blinding

This will be an open-label study.

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of CAB LA will be detailed in a Study Specific Technical Agreement/Memo (TTS) or Pharmacy Manual which will be accompanied by a Quality Agreement.

- Only subjects 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 labelled 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).
- Further guidance and information for final disposition of unused study treatment are provided in the Procedures Manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Study Treatment Administration

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff. When subjects 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 subject 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.

Study subjects will be dispensed CAB oral tablets during the lead-in period. When subjects self-administer study treatment(s) at home, compliance with oral CAB will be assessed through querying the subject during the site visits and documented in the source documents and CRF. Additional checks on adherence to study protocol will take place via pill count, home diaries, and periodic review of the diaries during study visits. A

record of the number of CAB tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays, will also be recorded in the CRF.

6.7. Treatment of Study Treatment Overdose

For the oral lead in period of this study, any dose of CAB > 30 mg within a 24 hour time period [± 4 hours] will be considered an overdose.

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

GSK does not recommend specific treatment other than supportive care for an overdose. The investigator will use clinical judgement to treat any overdose.

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

1. contact the Medical Monitor immediately
2. closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until CAB can no longer be detected systemically (at least 52 weeks for CAB LA).
3. obtain a plasma sample for pharmacokinetic (PK) analysis 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 subject.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy volunteers are eligible for study participation.

6.9. Lifestyle and/or Dietary Restrictions

6.9.1. Meals and Dietary Restrictions

An overnight fast is preferred prior to screening laboratory assessments; however, a minimum of a 6 hour fast is acceptable. Otherwise, food and drink can be given ad libitum throughout the course of the trial. At visits where subjects will be in the clinic for multiple hours, meals will be provided by the study site (in the form of a boxed lunch or card for use at the site cafeteria). Subjects will be asked to fast for 8 hours prior to the endoscopy procedures.

6.9.2. Alcohol

Subjects will abstain from alcohol for 48 hours prior to initiating oral dosing and prior to the injection. Subjects will abstain from alcohol for 48 hours prior to the collection of the pharmacokinetic sampling and clinical laboratory tests during each session.

6.9.3. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities while in the research clinic (e.g., watch television, read).

6.10. Concomitant Medications and Non-Drug Therapies

6.10.1. Permitted Medications and Non-Drug Therapies

Acetaminophen, at doses of ≤ 2 grams/day is permitted for use any time during the study. Concomitant medications (prescription and non-prescription) should be taken only as medically necessary during the study (except for prohibited medications described in Section 6.10.2). All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

6.10.2. Prohibited Medications and Non-Drug Therapies

Experimental agents not otherwise specified in the protocol, antiretrovirals, cytotoxic chemotherapy, or radiation therapy may not be administered. Systemically administered immunomodulators are prohibited. Chronic daily non-steroidal anti-inflammatory drug use for more than 14 days consecutively (with the exception of aspirin used for prophylaxis) is not permitted at any time during the study.

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

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

The following medications are anticoagulant/antiplatelet medications and could increase the risk of bleeding during biopsy procedures and interfere with the ability to receive intramuscular injections. Their use is prohibited within 7 days before and for 7 days after

the injection and biopsy procedures:

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

During the oral lead-in, oral CAB 30 mg should be administered 2 hours before or 6 hours after taking antacids, vitamins, calcium and iron supplements containing polyvalent cations (e.g., aluminium and magnesium).

7. STUDY ASSESSMENTS AND PROCEDURES

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

The following points must be noted:

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

3. Blood draws.

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

- The timing and number of planned study assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required
- Allowable time windows for study assessments can be found in the SRM.

7.1. Time and Events Table

7.1.1. Screening and Oral Lead-in Phase

Study Period	Screening[1]	Oral Lead-in[7]			Washout Period
		Dosing Days 1-28			
Visit Window	Within 30 days of oral lead-in	Day 1	Day 14	Day 29	14 – 42 days
Informed Consent	X				
Demographics	X				
Medical / Medication / Drug / Alcohol History	X				
Eligibility Assessment - Inclusion/Exclusion Criteria	X				
Height, Weight, BMI	X				
Physical Exam	X				
Vital Signs (Section 7.4.4)[2]	X	X	X	X	
12-Lead ECG (Section 7.4.5)	X	X	X		
Drug / Alcohol Screen (Section 7.4.6)[2]	X	X			
Pregnancy Test (Section 7.4.6)[2]	X	X		X	
Hepatitis B, Hepatitis C Screening (Section 7.4.6)	X				
HIV Test (Section 7.4.6)	X			X	
STD Screening (Section 7.4.6)	X				
Urine Dipstick Screening (Section 7.4.6)	X				
Hematology with differential; Clinical Chemistry Tests (Section 7.4.6)[2]	X	X	X	X	
Coagulation Tests (Section 7.4.6)	X			X	
Administer oral CAB[3]		X	X		
Dispense Oral lead-in IP		X			
Dispense Medication Dosing Diary		X			
Drug accountability/ pill count/review drug diary			X	X	
Blood plasma PK sampling				X	
Tissue/CVF/RF PK sampling[4]				X	
AE Assessment[5]		X	X	X	
Concomitant Medication Review		X	X	X	
PGx[6]		←		X	→

1. Screening may occur over more than one visit but within 30 days of the first dose of oral CAB 30 mg in the oral lead in phase.
2. Prior to administering the first oral dose of CAB, study personnel must verify the following pre-dose assessments to be within normal limits prior to administration: vital signs, pregnancy test (negative; FRP only). The results of the Drug/Alcohol screen, hematology with differential, and clinical chemistry tests on Day 1 are not required prior to administering the first oral dose of CAB 30 mg, but should be drawn prior to CAB administration.
3. Oral CAB dosing for Days 1 to 28. Day 29 assessments to be performed within 24 hours from the last dose on Day 28.
4. Female subjects may consent to have paired rectal tissue and rectal fluid samples collected at each time-point. Female subjects who do not wish to participate in rectal PK sampling may still participate in the study.
5. AE assessment will include a brief, symptom-directed physical exam as needed.
6. PGx: Can be collected any time; however, it is preferable to collect the sample at the earliest convenient time after the first dose in the oral lead in phase.
7. If a subject is withdrawn prior to receiving the CAB LA injection, a follow-up/withdrawal visit should be scheduled 10-14 days after the last oral dose of CAB.

7.1.2. CAB Injection, Compartmental PK Sampling, and Follow-up

Procedures	Day 1			Day 3	Day 5	Day 8	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52	Withdrawal[1]
	Pre-dose[2]	0 h	4h	48h	96h	168h							
Interim Medical / Medication / Drug / Alcohol History	X												
Brief Physical Exam (Section 7.4.3)	X												X
Vital Signs (Section 7.4.4)	X			X	X	X	X	X	X	X	X	X	X
Pregnancy Test (Section 7.4.6)	X						X	X	X	X	X	X	X
Hematology with differential; Clinical Chemistry Tests (Section 7.4.6)	X						X	X	X				X
HIV Test (Section 7.4.6)									X	X	X	X	X
STD testing (Section 7.4.6)	X												
Administer CAB LA 600 mg IM		X											
Injection Site Reaction Assessment		X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X			X	X	X	X	X	X	X	X	X	X
Blood plasma PK Sampling	X		X	X	X	X	X	X	X	X	X	X	X
Luminal Fluid (CVF/RF) PK Sampling[4]				X		X	X	X	X				
Tissue PK Sampling[4] (Table 4)				X[5]		X	X	X[5]	X				
MRI[6]		X		X		X							

1. Subjects who terminate before week 52 will be asked to return to the site for a withdrawal visit.
2. On Day 1, study personnel must verify the following pre-dose assessments to be within normal limits prior to injection: brief physical exam, vital signs, pregnancy test (negative; FRP only), AE assessment, and concomitant medication assessment. If a clinical abnormality, clinically significant AE, or prohibited medication that precludes injection is observed/recorded, the medical monitor must be contacted for further instruction.
3. AE assessment will include a brief, symptom-directed physical exam as needed.
4. Female subjects may consent to have paired rectal tissue and rectal fluid samples collected at each time-point. Female subjects who do not wish to participate in rectal PK sampling may still participate in the study.
5. Vaginal tissue will be collected only on Day 3 (48 hour) and Week 8.
6. Non-contrast MR Imaging will be performed in a subset of up to 8 subjects (4 males and 4 females). The MRI at 0h will be performed immediately after CAB injection and before the 4h blood plasma PK assessment.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

Written informed consent must be obtained from each potentially eligible subject (or his or her legal representative) by study site personnel **prior** to the initiation of any screening procedures as outlined in this protocol. The consent form must have been approved by the Institutional Review Board/Institutional Ethics Committee (IRB/IEC). After signing an informed consent, subjects will complete screening assessments to determine subject eligibility. Each subject being screened for study enrolment evaluation will be assigned a subject number. This number will be given sequentially in chronological order of subject presentation.

Subjects must be counseled on the practice of safer sexual practices including the use of effective barrier methods (e.g. male condom) for the length of time in which they are required for participation in this study as part of the eligibility process.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

7.3. Screening

All clinical and laboratory assessments of eligibility must be performed and reviewed within 30 days of initiating the oral lead-in phase. All Screening results must be available prior to enrollment.

Eligibility criteria must be carefully assessed at the Screening visit and confirmed at the Day 1 Oral lead-in phase visit and re-confirmed prior to injection.

Subjects may be enrolled and begin the oral lead-in phase as soon as all Screening assessments are complete and the results are available and documented.

Subjects who meet all entry criteria are enrolled and assigned a subject number. Subjects not meeting all inclusion and exclusion criteria at initial screen may be re-screened one time with a new subject number. Subjects who are enrolled into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

7.3.1. Baseline

Subjects will have “Baseline” assessments completed at Day 1 of the oral lead-in dosing period.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests such as vital signs, physical exams and laboratory safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

In order to monitor safety and to respond to occurrences of toxicity expeditiously, the team will hold conference calls on a regular basis during study implementation, and additional conferences calls will take place on an *ad hoc* basis. Study site investigators will be responsible for close monitoring and management of AEs, and will have detailed SOPs for the reporting of AEs and the management of toxicity. The Safety Monitor will be responsible for providing support to study investigators regarding the clinical management of individual participants (including decision-making surrounding eligibility, discontinuation/holds/termination of study drug, and clinical management).

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

The definitions of an AE or SAE can be found in Appendix 3 and Appendix 4. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0 (Section 12.4) will be employed to grade the severity of the detected adverse events.

For this study, the Sponsor considers seizures as an AE of special interest (see Investigator's Brochure for background information). Where seizures occur, the Sponsor would like to better characterize these occurrences to enable systematic analyses. Investigators are requested to document and report seizure or possible seizure events promptly (within 24 hours of learning of the event) to the Sponsor for evaluation and onward reporting. Data should be documented on the appropriate AE/SAE page (see Section 12.3).

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

7.4.1.1. Injection Site Reactions

Injection Site Reaction (ISR) examination will include an assessment of pain, tenderness, pruritus, warmth, infections, rash, erythema, swelling, induration, and nodules (granulomas or cysts). Digital photographs will be documented on all subjects who have an ISR that are Grade 2 if persistent beyond 2 weeks, any Grade 3 or above, or are serious. Dermatology will be consulted on all subjects who have an injection site reaction considered serious, Grade 3 or above, or if persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary.

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.4), at the timepoints specified in the Time and Events Table (Section 7.1).

- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3. The relatedness of a given AE to the study product will be assessed by study investigators as described in Appendix 3.

7.4.1.3. Method of Detecting AEs and SAEs

Study participants will be provided with a 24-hour telephone and pager number to contact site investigators, and will be encouraged to contact the study clinician/ investigator at the first sign of any adverse event they may experience. For life-threatening events, they will be instructed to seek immediate emergency care. If feasible, they will be asked to seek care at the facility where the site investigator is based, and to tell the medical staff to contact the site investigator upon their arrival there. Medical records from such encounters will be reviewed by study investigators after appropriate permissions are obtained from the subject, and data relating to potential adverse events will be entered into AE CRFs.

All AEs Grade I and higher will be recorded by study staff on source documents and the appropriate CRF. This will occur regardless of relatedness to study product.

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

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

7.4.1.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.1 and Section 12.3.4) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.4.1.5. Cardiovascular and Death Events

Any cardiovascular or death event, as defined in Section 12.3.3, will be reported to the SAE protocol contact and Medical Monitor. In the case of a cardiac event, the participant will be referred to the appropriate acute medical care.

7.4.1.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs, Including HIV Seroconversion

Disease-Related Events or Disease-Related outcomes in this case are not expected, as this will be a study in healthy volunteers. HIV screening will be performed at screening and at various points throughout the study. Individuals with one or more reactive test will be ineligible to participate in the study. Furthermore, individuals with signs of acute retroviral syndrome at screening or enrollment (temperature >101 degrees, lymphadenopathy, pharyngitis, myalgias/arthralgias) will not be enrolled. During subsequent study visits, individuals who develop signs or symptoms of acute retroviral syndrome will be re-screened with serum HIV RNA PCR.

In the case of the detection of HIV by screening test, confirmatory testing will be performed. See Appendix 6. If HIV seroconversion occurs during the study, the subject will be informed of these results and referred for appropriate care, and the event will be immediately reported to the Sponsor and to the relevant division of the State Department of Health. If HIV seroconversion occurs after the CAB LA IM injection, immediate suppressive ART will be facilitated to prevent the possible development of resistance on monotherapy. This will be continued for a minimum of 52 weeks post IM injection.

In the case of a subject reporting a high-risk HIV exposure, the provision of post exposure prophylaxis will be expedited at the site level. If in the oral phase, no further study drug will be given. However, if the IM CAB LA has already been received, safety assessments and monitoring will be continued for 52 weeks after injection or until the study product is no longer detectable in plasma, whichever is longer. Furthermore, any possible exposure to HIV that occurs during the study, as identified by the study participant, must be reported to the study investigators, Sponsor, and Safety Monitor.

7.4.1.7. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs, AEs of special interest (i.e. seizures, see Section 7.4.1) and non-serious AEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

7.4.2. Pregnancy

As outlined in the Inclusion Criteria, all female participants of reproductive potential are required to use an effective contraceptive method for the duration of the study, as well as condoms (male or female) for the prevention of STIs. Contraceptive counseling will be provided on an as-needed basis to participants, and study staff will make the appropriate referrals to sources of reproductive care.

As outlined in the Time and Events Table (Section 7.1), female participants of reproductive potential will have pregnancy testing performed; they will also be encouraged to report all signs or symptoms of pregnancy to study staff. Any pregnancy that occurs during female subjects' participation in the study will be reported to the Sponsor and Safety Monitor immediately upon site awareness and confirmed with serum pregnancy testing.

If a subject should become pregnant during the oral lead-in phase, the study product will be immediately discontinued and the subject will continue to be followed for safety evaluations every 4-5 weeks until the pregnancy outcome is reached, at which point the subject will be terminated from the study. If a subject should become pregnant at any time point after the IM CAB LA injection has been received, she will continue on study and will receive the appropriate safety follow-up evaluations including plasma PK, per the Time and Events Table.

The site or designee will counsel any participants who become pregnant regarding possible risks to the fetus according to site-specific SOPs. Participants may not enroll if they are currently breastfeeding and study product should be discontinued if any participant identifies that she is breastfeeding after enrollment. The site or designee also will refer the participant to the appropriate care.

- Details of all pregnancies in female subjects will be collected after the start of dosing and until the last follow-up assessment.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

- All pregnancy outcomes will be reported on relevant Case Report Forms (CRFs). Outcomes meeting criteria for expedited adverse event (EAE) reporting also will be reported.

7.4.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Skin, Cardiovascular, Respiratory, Gastrointestinal, Genitourinary, and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

7.4.4. Vital Signs

- Vital signs will be measured in semi-supine position after 10 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.
- Single blood pressure (BP) and heart rate (HR) measurements will be taken on Day 1 of the oral lead-in and will be classified as baseline. A single repeat measurement is allowed to determine eligibility. Single BP and HR measurements will be obtained at all other timepoints during the study.

7.4.5. Electrocardiogram (ECG)

- 12-lead ECG will be performed with the subject in a semi-supine position having rested in this position for at least 10 minutes beforehand.
- 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. A single repeat measurement is allowed to determine eligibility.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 5, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments. An overnight fast is preferred prior to screening laboratory assessments; however, a minimum of a 6 hour fast is acceptable.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

A single repeat laboratory test will be allowed for eligibility. Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 5.

Table 5 Protocol Required Safety Laboratory Assessments

Laboratory Assessments[1]	**Parameters**			
Hematology with differential	Platelet Count	*RBC Indices*:	*WBC absolute count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit	MCHC	Monocytes	
			Eosinophils	
			Basophils	
			Immature band forms	
Coagulation Tests	PT	PTT	INR	
Clinical Chemistry Tests [2]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	CPK			
Routine Urine dipstick with reflex urinalysis if abnormal	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
STD Screen[3]	• Gonorrhoea • Chlamydia • Syphilis • Trichomonas			
Other Screening Tests	• HIV: HIV 1-2 Ab/Ag testing • Hepatitis B screen: Hepatits B surface antigen (HBsAg) Hepatitis B surface antibody(HBsAb), and Hepatitis core antibody (HBcAb) • Hepatitis C (Hep C antibody) • Alcohol screen and drugs of abuse screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine (or serum) hCG Pregnancy test (as needed for women of child bearing potential)[4]			

NOTES:

1. An overnight fast is preferred prior to screening laboratory assessments; however, a minimum of a 6 hour fast is acceptable.
2. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.1 and Appendix 2.
3. STD screening tests will be performed per local site standards. Preferably, urine should be sent for nucleic acid testing (NAAT) for gonorrhea (GC), Chlamydia and trichomonas, and a rectal swab should be sent for NAAT for GC and Chlamydia. For syphilis screening, a plasma RPR will suffice.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee or site preference.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 52 weeks after the last dose of study treatment

should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4.7. Magnetic Resonance Imaging

Non-contrast-enhanced MRI imaging will be performed after injection at the timepoints outlined in the Time and Events Table (Section 7.1) in a subset of up to 4 females and 4 males to assess evolution of injection depot localization. Subjects will undergo a MRI scanning session in the prone position not to exceed 60 minutes. The scanning duration will be designed to be approximately 30 minutes. No contrast agents will be used. All scanning sessions for an individual subject should occur on the same scanner. A reference phantom may be placed next to the subject to allow for signal normalization between visits.

The scanning procedures will consist of routine localizers followed by an examination of the injection depot in the gluteal muscle. Further details of the scanning protocol will be provided in a dedicated Imaging Manual. MRI images and quantitative assessments will be collected and reported separately by GSK Platforms Technology Sciences.

All MRI scans will be reported (non-anonymized) for clinical abnormalities.

7.5. Pharmacokinetics

Blood samples for plasma pharmacokinetic (PK) analysis of CAB will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. With the exception of PK sampling in the first week post-injection which should be performed according to schedule, the timing of PK sample collection may be altered (±3 days) for scheduling purposes if deemed appropriate by the investigator in consultation with the sponsor.

Blood samples (4 mL each) will be collected into potassium EDTA tubes for plasma CAB analysis, and initial processing will take place as follows:

Immediately after collection, gently invert (DO NOT SHAKE) the evacuated blood collection tube 8-10 times to mix the Potassium Ethylenediaminetetraacetic acid (potassium EDTA) anticoagulant with the whole blood and place the sample(s) on ice.

Within 1 hour of sample collection, separate the plasma by refrigerated (4°C) centrifugation at 1,500 to 2,000 x g for a minimum of 10 minutes.

Immediately after sample processing freeze the plasma storage tubes in the upright position in a non-self-defrosting freezer. Store at -20°C or lower until transfer to bioanalytical facility.

Vaginal, cervical and rectal tissue biopsies and luminal (cervicovaginal and rectal) fluid collections will be done at the time points indicated in Section 7.1. At each female genital tissue sampling time point, up to 3 vaginal and 3 cervical biopsies will be collected via speculum exam per subject. At each rectosigmoid tissue sampling time

point, up to 10 biopsies will be collected at 15 cm from the anal margin via flexible sigmoidoscopy. Details outlining the collection and processing of tissue/ CVF/RF can be found in the SRM.

7.5.1. Sample Analysis

Plasma/tissue/luminal fluid analysis will be performed by the Clinical Pharmacology Analytical Laboratory (CPAL) at Johns Hopkins University and under the management of GSK PTS/BIB. The details of sample collection and analysis will be included in the SRM and additionally in the study sample analysis plan. Concentrations of CAB will be determined in samples using the currently approved bioanalytical methodology. Raw data will be stored at the bioanalytical site. Validation testing will be performed in accordance with the FDA Bioanalytical Method Validation Guidance for Industry and assays reviewed in accordance with the NIH-cross network Clinical Pharmacology Quality Assurance (CPQA) program.

Once the blood plasma/tissue/CVF/RF sample has been analyzed for CAB any remaining sample may be analyzed for other compound-related metabolites or to further understand the compound or the disease being studied and the results reported under a separate protocol and analysis plan.

7.6. Genetics

6 mL of blood will be collected into an EDTA tube for future pharmacogenomic analysis. Information regarding pharmacogenetic (PGx) research is included in Appendix 8. The IRB/IEC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and in most cases, the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

8. DATA MANAGEMENT

- For this study, subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- For this study subject data will be collected using GSK defined case report forms and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

- Original CRFs will be retained by GSK, while the investigator will retain a copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objectives of this study are to assess the pharmacokinetics of CAB LA in blood plasma and vaginal, cervical, and rectal tissues and secretions following a single 600 mg intramuscular dose. No formal statistical hypotheses are to be tested. Where appropriate, an estimation approach will be taken, and point estimates and confidence intervals will be constructed. There will be no formal comparison.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

There was no formal calculation of power or sample size for this study.

Approximately 20 healthy subjects from up to two clinic sites will be enrolled in oral lead-in phase such that approximately 16 evaluable subjects (8 males and 8 females) will receive a CAB IM injection and complete 12 weeks of PK sampling.

Based upon the pharmacokinetic data generated in previous pharmacokinetic tissue studies and the complexity and intensity of sampling of plasma and tissue in this study, the proposed sample size of 16 evaluable subjects (8 women and 8 men) will allow for an informative assessment and description of pharmacokinetic parameters.

9.2.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Safety Population

All subjects enrolled in the study who have received at least one dose of study drug will be included in the Safety Population.

Pharmacokinetic Concentration Population

The PK Concentration Population will include all subjects who undergo plasma and compartmental PK sampling and have evaluable PK assay results. This population will be used for the concentration listing.

Pharmacokinetic Parameter Population

The PK Parameter Population will include all subjects who undergo plasma and compartmental PK sampling and have evaluable CAB PK parameters estimated. This population will be used for PK parameter listing, plotting of the concentration-time data and PK parameter summary.

9.3.2. Interim Analysis

There will be no formal interim analysis; however preliminary CAB LA PK parameters may be generated and reviewed internally at GSK to assess the current CAB LA batch being used in this study (Section 6.1.2) relative to historical data.

9.4. Key Elements of Analysis Plan

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation Department within GSK. All PK data will be stored in the Archives, GSK Pharmaceuticals, R&D.

Statistical analyses of the PK parameter data will be the responsibility of Clinical Statistics, GSK.

Data will be listed and summarized according to GSK reporting standards, where applicable. Listings will be sorted by subject, Phase, day, and time, noting treatment; summaries will be presented by treatment, gender and overall.

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

9.4.1. Primary Analyses

Primary endpoints include CAB concentrations in blood plasma and in VT, CT, CVF, RT and RF (as data permit) in women and RT and RF in men up to Week 12. These concentrations will be determined directly from concentration-time data from each matrix. Descriptive statistics and graphics will be created to describe the primary PK endpoints of interest.

9.4.2. Secondary Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Plasma and tissue/fluid concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.2 or higher (Pharsight, Inc., Cary, NC). Pharmacokinetic parameters will be estimated via noncompartmental analysis using the linear up/log down application of the trapezoidal rule for model 200 (extravascular administration) of the

WinNonlin program. Calculations will be based on the actual sampling times recorded during the study. The following PK parameters will be calculated if available:

• CVF:BP, CT:BP, VT:BP, CT:CVF, VT:CVF ratio in women and, RT:BP, and RT:RF ratios in males and females at matching time points where data permit during the injection phase.
• Cmax,tmax, AUC(0-∞), AUC(0-last), AUC(0-Wk4), AUC(0-Wk8) and AUC(0-Wk12) and t½ in blood plasma and in CT, and CVF in females and RT and RF in males and females. • Ratios of time-matched AUCs tissue matrices/luminal fluid: blood plasma where data permit.
• CAB concentration in VT, CT, CVF, RT, RF and BP on Day 29 of the oral lead-in phase prior to IM injection

Ratios will be calculated for each subject. Evaluable PK parameters and calculated ratios will be summarized by gender and/or overall for each matrix. A sex-based comparison will be made for all the evaluable blood plasma PK parameters and estimated ratio between females vs males and its associated 90% CI will be provided. Covariates of BMI and other factors may also be considered in the model for the blood plasma PK parameter comparison. CAB concentration in each matrix from the oral lead-in phase may be compared with Weeks 4, 8, and 12 concentrations if data permit. The relationship between the plasma CAB PK concentration with time matched CVF, CT, VT, RT and/or RF will be assessed with plots and by the SAS Proc Corr procedure.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

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

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- ViiV/GSK will provide full details of the above procedures, either verbally, in writing, or both.

- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

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

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

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

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

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, ViiV/GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and ViiV/GSK Standard Operating Procedures.
- ViiV reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If ViiV determines such action is needed, ViiV will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, ViiV will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, ViiV will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. ViiV will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a ViiV/GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- ViiV/GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any

institutional requirements or local laws or regulations, ViiV/GSK standards/procedures, and/or institutional requirements.

- The investigator must notify ViiV/GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

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 subjects, 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.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC(0-last)	Area under the concentration time curve from time zero to last quantifiable time point
AUC(0-∞)	Area under the concentration time curve from time zero to infinity
AUC(0-Wk4)	Area under the concentration time curve from time zero to Week 4
AUC(0-Wk8)	Area under the concentration time curve from time zero to Week 8
AUC(0-Wk12)	Area under the concentration time curve from time zero to Week 12
Cτ	Steady-state pre-dose CAB concentration
CMP	complete metabolic panel
CPAL	Clinical Pharmacology Analytical Laboratory (JHU)
CPK	Creatine phosphokinase
CT	cervical tissue
CVF	cervicovaginal fluid
C48h	Concentrations observed at Day 3 (48h)
Cd8	Concentration observed on Day 8
CWk4	Concentration observed at Week 4
CWk8	Concentration observed at Week 8
CWk12	Concentration observed at Week 12
DBili	direct bilirubin
FRP	females of reproductive potential
GSK	GlaxoSmithKline
HDPE	high density polyethylene
HIV	human immunodeficiency virus
IC_{90}	90% maximal inhibitory concentration
IEC	independent ethics committee
IM	intramuscular(ly)
INR	international normalized ratio
INSTI	Integrase strand transfer inhibitor
IP	investigational product

IRB	institutional review board
ISR	injection site reaction
JHU	Johns Hopkins University
LA	long-acting
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
NHP	non-human primate
PK	pharmacokinetic(s)
PrEP	Pre-exposure prophylaxis
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
RF	rectal fluid
RNA	ribonucleic acid
RT	rectal tissue
SHIV	simian/human immunodeficiency virus
SRM	Study reference manual
SOP	standard operating procedure
t½	apparent terminal phase half-life
TBili	total bilirubin
VT	vaginal tissue
WBC	white blood cell

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by ViiV Healthcare
Parexel
SAS
WinNonlin

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>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="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• 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 subject 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 subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is 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</td><td>• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake 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).
• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
• Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	definite or likely acetaminophen use in the preceding week [James, 2009]. • Referral for the appropriate care, including Liver imaging (ultrasound, magnetic resonance, or computerised tomography) ± liver biopsy; complete Liver Imaging and/or Liver Biopsy CRF forms.

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

Phase I liver chemistry stopping criteria and required follow up assessments

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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 subjects receiving anticoagulants
3. Includes: 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. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject'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, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject'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 subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.3.3. Definition of Cardiovascular Events

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

- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4. AEs of Special Interest:

Seizures:

Three cases of seizures have occurred in the CAB program cumulatively through 01 October 2015. ViiV Healthcare has reviewed these cases in detail and does not believe they constitute a reasonable likelihood of causation associated with CAB. This assessment is supported by the lack of preclinical signal, class effect or known CNS mechanism, the relatively low frequency of seizures relative to expected rates in both healthy and HIV positive subjects and clinical confounders in each case.

Where seizures occur, the Sponsor would like to better characterize these occurrences to enable systematic analyses. Investigators are requested to document and report seizure or possible seizure events promptly (within 24 hours of learning of the event) to the Sponsor for evaluation and onward reporting. Data should be documented on the appropriate AE/SAE page.

12.3.5. Recording of AEs and SAEs

AEs and SAE Recording:

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

12.3.6. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

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

Reporting of SAEs to GSK

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

12.4. Appendix 4: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Averse Events Version 2.0, November 2014

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
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 not 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 OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
CARDIOVASCULAR				
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE AND METABOLIC				
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
GASTROINTESTINAL				
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
MUSCULOSKELETAL				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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				
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	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				
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)

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
SENSORY				
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 Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
SYSTEMIC				
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	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[10] (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[11]	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[12] *> 5 to 19 years of age*	NA	WHO BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	NA	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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
< 2 years of age	NA	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
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)
URINARY				
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				
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[13] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm2 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
LABORATORY VALUES Chemistries				
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin *Direct Bilirubin[14], High* *> 28 days of age*	NA	NA	> ULN	> 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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	≥ 5.0 x ULN
≤ 28 days of age	Total Bilirubin for Term and Preterm Neonates	Total Bilirubin for Term and Preterm Neonates	Total Bilirubin for Term and Preterm Neonates	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*
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 < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance[15] or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from 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*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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*
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*
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[16], 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 *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*
Hematology				
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age* *(not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥ 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*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
≥ 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*
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/mm3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 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*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
≤ *7 days of age*	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*
Urinalysis				
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

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.
2. As per Bazett's formula.
3. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
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.
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.
7. Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
8. Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.
9. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
11. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12. WHO reference tables may be accesed 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.
13. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
14. 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.
15. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m_2).
16. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
17. Male and female sex are defined as sex at birth.
18. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. 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 the appropriate conversion factor for the particular laboratory.

12.5. Appendix 5: 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:

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

If the additional tests are within the normal range, subjects may continue study medication. If one or more of the additional tests is abnormal or suggestive of hemolytic anemia as specified above, subjects will permanently discontinue study medication and be withdrawn from the trial. Subjects 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:

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

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

- peripheral blood smear
- indirect bilirubin
- haptoglobin
- reticulocyte count

Subjects will permanently discontinue study medication and be withdrawn from the trial. Consultation with a Hematologist should be considered. Subjects 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). Subjects may continue study medication. Subjects 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). Subjects will permanently discontinue study medication and be withdrawn from the trial. Subjects should be followed up until resolution (return to baseline) of bilirubin elevation.

AST AND ALT ELEVATION

See Appendix 2.

RASH

Grade 1 rash (Localized macular rash):

Subjects 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:

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

In the absence of the above signs or symptoms, subjects with Grade 1 rash may continue the study drug at the discretion of the Investigator. The subject 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 subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in the Time and Events table.

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

Subjects 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, subjects 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 subject 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 subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in the Time and Events table.

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):

Subjects with a Grade 3 rash will permanently discontinue the study medication. The subject 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 subject 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 subject should remain on the study to be followed for safety and PK as outlined in the Time and Events table.

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)):

Subjects 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 GSK Medical Monitor should be notified of this serious adverse event within 24hr via phone or fax or email. The subject should be closely followed everyday until resolution of the reaction. The subject should remain on the study to be followed for safety and PK as outlined in Time and Events table.

ALLERGIC REACTION

Grade 1 allergic reaction (Pruitis without rash):

Subjects 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:

- Temperature > 38.5°C
- Eosinophilia
- Respiratory involvement including bronchospasm, laryngospasm, or angioedema
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 1 allergic reaction may continue the study drug at the discretion of the Investigator. The subject 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 subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in the Time and Events table.

Grade 2 allergic reaction (Localized urticaria):

Subjects 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:

- Temperature > 38.5°C
- Eosinophilia
- Respiratory involvement including bronchospasm, laryngospasm, or angioedema
- Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 2 allergic reaction may continue the study drug at the discretion of the Investigator. The subject 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 subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and PK as outlined in the Time and Events table.

Grade 3 allergic reaction (Generalized urticaria or angioedema):

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

Grade 4 allergic reaction (Anaphylaxis):

Subjects will permanently discontinue the study medication and be withdrawn from the trial. Subjects will be treated as clinically appropriate. Subjects 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

12.6. Appendix 6: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- Oral Phase: Will cease to have any drug administered, but will continue to receive safety, clinical and laboratory monitoring to minimize further exposure to the fetus.
- Injection Phase: will continue to receive safety, clinical and laboratory monitoring through the completion of the pregnancy.

12.7. Appendix 7: 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
HIV Counseling	X
Offer Condoms	X
Clinical Evaluations and Procedures	
Blood collections for plasma storage[1]	X
Schedule Follow-up Visits[2]	X
CD4 Cell Count[3]	X
HIV Viral Load[3]	X
HIV Resistance Testing[3]	X

(1) Stored plasma samples will be collected from participants who acquire HIV infection, these assessments may include PK assessment, 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) Subjects will continue to be followed at the same frequency as regular study visits. (Section 7.1).
(3) Sites will collect specimens for testing at Quest and have the option to also send samples to a local laboratory to assist with clinical management.

12.8. Appendix 8: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

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

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- HIV susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample

destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

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

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

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

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

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

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

References

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.9. Appendix 9: Protocol Amendment Changes

Amendment 3: Effective Date 14-AUG-2017

This amendment applies to all subjects who will participate in the study.

Summary of Amendment Changes with Rationale

In addition to minor edits, updated the wash-out period between oral and LA dosing to accommodate visit scheduling, and removed the needle length and specification for intramuscular injection in Section 6.1.3.

List of Authors

PPD was added to the list.

Medical monitor/Sponsor Information Page

Rationale :

Medical monitor/SAE Contact information was updated to reflect the current medical monitor.

PREVIOUS TEXT

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD, MD	PPD			ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709
Secondary Medical Monitor	PPD, MD				ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709
Tertiary Medical Monitor	PPD, MD, MPH				ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709

REVISED TEXT

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD , DO, MSc	PPD			ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709
Secondary Medical Monitor	PPD , MD				ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709
Tertiary Medical Monitor	PPD , MD				ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709

Section 4.1 Overall Design

Rationale:

Washout period is updated to aid the sites flexibility with the scheduling.

The duration of washout period is being updated from 14-21 days to 14-42 days.

This change is made consistently throughout the document.

Section 4.2 Treatment Arms and Duration

Rationale:

Due to the longer washout period, the study duration is updated from up to 62 weeks to 66 weeks.

PREVIOUS TEXT

Each subject will participate in the study for approximately up to **62** weeks.

REVISED TEXT

Each subject will participate in the study for approximately up to **66** weeks.

Section 4.1.4 Follow-up/Withdrawal Visit

Rationale:

The following text was added to clarify on the follow up after receiving the CAB LA injection.

ADDITIONAL TEXT:

If a subject is withdrawn or disqualified from the study after receiving the CAB LA injection, because of the long acting pharmacokinetic profile of CAB LA every effort should be made to bring the subject back in for the 52 weeks of safety and PK assessments following the injection.

Section 5.1 Inclusion Criteria

Rationale:

The list of contraceptives was updated to make it consistent with the current program list in inclusion criterion #6.

REMOVED TEXT:

- Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]:

Section 5.4 Withdrawal/Stopping Criteria

Rationale:

A clarification is made for the subjects withdrawing after the LA injection.

PREVIOUS TEXT

Once a subject has received the IM injection of CAB LA, they will be followed per protocol for appropriate procedures and safety evaluations, and will not be removed from the study for medical reasons, unless they refuse to continue participation.

REVISED TEXT

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

Section 5.5 Subject and Study Completion

Rationale:

The duration for the completer for PK assessments is updated to 12 weeks from 8 weeks to align with the duration for primary objective.

PREVIOUS TEXT

A subject that receives the CAB LA injection and completes the PK assessments for **8** weeks but withdraws prior to the 52 week follow up visit, will be considered completing the treatment phase of the study, but not a study completer.

A subject that withdraws after injection and does not complete PK assessments through week **8** is considered a non-completer for treatment and study. Because of the long acting pharmacokinetic profile of CAB LA every effort should be made to bring the subject back in for the 52 weeks of safety and PK assessments following the injection.

REVISED TEXT

A subject that receives the CAB LA injection and completes the PK assessments for **12** weeks but withdraws prior to the 52 week follow up visit, will be considered completing the treatment phase of the study, but not a study completer.

A subject that withdraws after injection and does not complete PK assessments through week **12** is considered a non-completer for treatment and study. Because of the long acting pharmacokinetic profile of CAB LA every effort should be made to bring the subject back in for the 52 weeks of safety and PK assessments following the injection.

Section 6.1.3 Dosing Considerations for CAB LA

Rationale:

The needle specifications are removed for the syringe, the details of which are provided in Study Reference Manual (SRM).

PREVIOUS TEXT

After cleaning the skin with alcohol swab, under direct ultrasound visualization, a 9-cm long, 25-gauge spinal needle will be introduced into the gluteal muscle. Then 600 mg CAB LA (concentration = 200 mg/mL (3mL) will be injected as a single IM injection slowly under continuous ultrasound visualization

REVISED TEXT

After cleaning the skin with alcohol swab, under direct ultrasound visualization~~, a 9-cm long, 25~~**22**-gauge spinal needle will be introduced into the gluteal muscle. Then 600 mg CAB LA (concentration = 200 mg/mL (3 mL) will be injected as a single IM injection slowly under continuous ultrasound visualization.

Section 7.1.1 Screening and Oral Lead-in Phase

Rationale:

The footnote was added as number 7 to clarify withdrawal visit in oral cycle to align with the withdrawal criteria.

ADDITIONAL TEXT:

7. If a subject is withdrawn prior to receiving the CAB LA injection, a follow-up/withdrawal visit should be scheduled 10-14 days after the last oral dose of CAB.

Section 12.4 Appendix 4

Rationale:

The title was updated to reflect Version 2.0, as the removed text was applicable to old DAIDS Version 1.0.

PREVIOUS TEXT

Section 12.4 Appendix 4: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Averse Events Version 2.0, November 2014; Clarification August 2009

REVISED TEXT

Section 12.4 Appendix 4: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Averse Events Version 2.0, November 2014~~; Clarification August 2009~~

Amendment 2: Effective Date 30-MAR-2016

This amendment applies to all subjects who will participate in the study.

Summary of Amendment Changes with Rationale

Section 3 Objectives and Endpoints

Primary endpoint:

PREVIOUS TEXT

- Concentrations observed at Day 3 (C48h), Week 1 (CWk1),Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) in blood plasma and in VT, CT, and CVF in women, and in RT and RF in men and women (as data permit) following a single CAB 800 mg intramuscular (split injection) dose.

REVISED TEXT

- Concentrations observed at Day 3 (C48h), Day 8 (Cd8),Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) in blood plasma and in CT, and CVF in women, and in RT and RF in men and women (as data permit) following a single CAB 600 mg intramuscular dose.
- VT concentrations observed at Day 3 (C48h), and Week 8 (CWk8), in women following a single CAB 600 mg intramuscular dose.

Secondary Endpoints

PREVIOUS TEXT

Concentration ratios including VT:blood plasma, CT:blood plasma, CVF:blood plasma, CT:CVF, VT:CVF in women, and RT:blood plasma, RF:blood plasma and RT:RF in men and women (as data permit) at C48h, CWk1, CWk4, CWk8, and CWk12

REVISED TEXT

Concentration ratios including VT:blood plasma, CT:blood plasma, CVF:blood plasma, CT:CVF, VT:CVF in women, and RT:blood plasma, RF:blood plasma and RT:RF in men and women (as data permit) **at matched timepoints evaluated.**

The following Secondary Endpoint was added.

- Tissue:blood plasma and fluid:blood plasma ratio of AUCs of intervals specified above.

Section 4.4 Design Justification

This section was updated to reflect current data and updated dosing of CAB LA.

CAB LA Dosing

Based on available data provided in Section 4.5, CAB LA dose of 800 mg (2 x 400 mg) was updated to single dose of 600 mg for the study. As a result, following sections were updated with the dosing

- Section 4.5 dose justification to reflect current data.
- Section 6.1 to indicate formulation and dosing changes.
- Section 9, dosing changes were made.

Requirement for Vaginal Tissue sampling

The requirement of vaginal tissue sampling was reduced to only Day 3 (48h) and Week 8. Accordingly, the changes were made to objectives and endpoint and sampling assessment tables.

Section 4.6.1 Benefit: Risk Assessment

This section was updated to reflect updated current CAB safety profile.

4.6.1 Table was updated.

4.6.1.1 Other Clinical Relevant Information was added.

Section 5.2 Exclusion Criteria

Exclusion criterion number 15 for hepatitis B and hepatitis C were separated into number 15 and 16, as per below.

PREVIOUS TEXT

15. Presence of hepatitis B surface antigen (or positive hepatitis B core antibody with negative hepatitis B surface antibody) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.

REVISED TEXT

15. Positive hepatitis B surface antigen, or a positive hepatitis B core antibody with negative hepatitis B surface antibody) test result at screening or within 3 months prior to first dose of study treatment.

16. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment

Section 5.4 Withdrawal/Stopping Criteria

Section 5.4.2 for QTc Stopping Criteria was added.

Section 5.5 Subject and Study Completion

PREVIOUS TEXT

A subject that receives the CAB LA injection and completes the PK assessments for 12 weeks but withdraws prior to the 52 week follow up visit, will be considered completing the treatment phase of the study, but not a study completer.

REVISED TEXT

A subject that receives the CAB LA injection and completes the PK assessments for **8 weeks** but withdraws prior to the 52 week follow up visit, will be considered completing the treatment phase of the study, but not a study completer.

Section 7.1 Time and Events Table

Section 7.1.1 Screening and Oral Lead-in Phase

Day 28 assessments were updated to Day 29, day after the last oral dose of CAB.

Day 14 hematology and chemistry tests were added, and Day 14 liver tests were removed.

Section 7.1.2 CAB injection, Compartmental PK Sampling, and Follow-up

Liver tests were deleted, and Pre-dose Day 1 hematology and chemistry tests were added.

Section 7.4.1 Adverse Events (AE) and Serious Adverse Events (SAEs)

Following text was added

For this study, the Sponsor considers seizures as an AE of special interest (see Section 12.3.4 for background information). Where seizures occur, the Sponsor would like to better characterize these occurrences to enable systematic analyses. Investigators are requested to document and report seizure or possible seizure events promptly (within 24 hours of learning of the event) to the Sponsor for evaluation and onward reporting. Data should be documented on the appropriate AE/SAE page (see Section 12.3.).

Section 7.4.3 Physical Exams

PREVIOUS TEXT

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal, Genitourinary, and Neurological systems. Height and weight will also be measured and recorded.

REVISED TEXT

- A complete physical examination will include, at a minimum, assessment of the **Skin,** Cardiovascular, Respiratory, Gastrointestinal, Genitourinary, and Neurological systems. Height and weight will also be measured and recorded.

Section 7.4.4 Vital Signs

Respiratory rate was removed.

- Vital signs will be measured in semi-supine position after 10 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate ~~and respiratory rate.~~

Section 7.4.6 Clinical Safety Laboratory Assessments

Clarification for STD Screen in Table 5 was added in the footnote.

Section 7.4.7 Magnetic Resonance Imaging

Following text was deleted:

Subjects will be asked to undergo MRI imaging on a first come first serve basis until 8 subjects (4 females and 4 males) consent to participate or until the primary study is fully enrolled, whichever comes first.

Section 7.5 Pharmacokinetics

PREVIOUS TEXT

Blood samples (4 mL each) will be collected into K3EDTA tubes for plasma CAB analysis, and initial processing will take place as follows:

REVISED TEXT

Blood samples (4 mL each) will be collected into **potassium** EDTA tubes for plasma CAB analysis, and initial processing will take place as follows:

Section 7.5 Pharmacokinetics

PREVIOUS TEXT

Vaginal, cervical and rectal tissue biopsies and luminal (cervicovaginal and rectal) fluid collections will be done at the time points indicated in Section 7.1. At each tissue sampling time point, up to 5 vaginal, 5 cervical, or a combination of 5 biopsies from both sites (5 total cervicovaginal biopsies) will be collected via speculum exam per subject. At each tissue sampling time point, up to 30 biopsies will be collected from the rectosigmoid via flexible sigmoidoscopy.

REVISED TEXT

Vaginal, cervical and rectal tissue biopsies and luminal (cervicovaginal and rectal) fluid collections will be done at the time points indicated in Section 7.1. At each female genital tissue sampling time point, up to **3** vaginal and **3** cervical biopsies will be collected via speculum exam per subject. At each rectosigmoid tissue sampling time

point, up to **10** biopsies will be collected at **15 cm from the anal margin** via flexible sigmoidoscopy.

Section 9.4.2 Secondary Analyses

PREVIOUS TEXT

• CVF:BP, CT:BP, VT:BP, CT:CVF, VT:CVF ratio in women and, RT:BP, and RF:RT ratios in males and females at 48hr, Weeks 1, 4, 8, and 12 during the injection phase.
• Cmax and tmax in all matrices • AUC(0-∞), AUC(0-last), AUC(0-Wk4)), AUC(0-Wk8), and t½ in blood plasma. • AUC(0-Wk12) in blood plasma and in VT, CT, and CVF in females and RT and RF in males and females. • Ratio of AUC(0-Wk12) tissue matrices/luminal fluid: blood plasma.
• Steady-state pre-dose CAB concentration (Cτ) in VT, CT, CVF, RT, RF and BP on Day 28 of the oral lead-in phase prior to IM injection

REVISED TEXT

• CVF:BP, CT:BP, VT:BP, CT:CVF, VT:CVF ratio in women and, RT:BP, and RT:RF ratios in males and females at matching time points where data permit during the injection phase.
• Cmax,tmax, AUC(0-∞), AUC(0-last), AUC(0-Wk4), AUC(0-Wk8) and AUC(0-Wk12) and t½ **in** blood plasma and in CT, and CVF in females and RT and RF in males and females. • Ratios of time-matched AUCs tissue matrices/luminal fluid: blood plasma where data permit.
• CAB concentration in VT, CT, CVF, RT, RF and BP on Day 29 of the oral lead-in phase prior to IM injection

Section 9.4.2 Secondary Analyses

Following statements were added.

Ratios will be calculated for each subject. Evaluable PK parameters and calculated ratios will be summarized by gender and/or overall for each matrix.

Covariates of BMI and other factors may also be considered in the model for the blood plasma PK parameter comparison. CAB concentration in each matrix from the oral lead-in phase may be compared with Weeks 4, 8, and 12 concentrations if data permit.

Section 12.3.4 AEs of Special Interest

Following information was added.

Seizures:
Three cases of seizures have occurred in the CAB program cumulatively through 01 October 2015. ViiV Healthcare has reviewed these cases in detail and does not believe they constitute a reasonable likelihood of causation associated with CAB. This assessment is supported by the lack of preclinical signal, class effect or known CNS mechanism, the relatively low frequency of seizures relative to expected rates in both

healthy and HIV positive subjects and clinical confounders in each case.

Where seizures occur, the Sponsor would like to better characterize these occurrences to enable systematic analyses. Investigators are requested to document and report seizure or possible seizure events promptly (within 24 hours of learning of the event) to the Sponsor for evaluation and onward reporting. Data should be documented on the appropriate AE/SAE page.

Amendment 1 – Effective Date 10-NOV-2015

Where the Amendment Applies

This amendment applies to all subjects who will participate in the study.

Summary of Amendment Changes with Rationale

Amendment 1 includes additional exclusion criteria for subjects with history of seizure disorder.

List of Specific Changes

Medical Monitor/SAE Contact Information:

PREVIOUS TEXT

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD , MD	PPD			GlaxoSmithKline 5 Moore Drive, Research Triangle, NC 27709
Secondary Medical Monitor	PPD , MD				GlaxoSmithKline 5 Moore Drive, Research Triangle, NC 27709
Tertiary Medical Monitor	PPD , MD, MPH				GlaxoSmithKline 5 Moore Drive, Research Triangle, NC 27709

REVISED TEXT

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD , MD	PPD			ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709
Secondary Medical Monitor	PPD , MD				ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709

Tertiary Medical Monitor	PPD , MD, MPH	PPD	ViiV Healthcare 5 Moore Drive, Research Triangle, NC 27709

Section 4.6.1 Risk Assessment

PREVIOUS TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK1265744/Cabotegravir		
Elevated liver transaminases	In ongoing Phase 2 HIV treatment studies with CAB (LAI116482, 200056) three subjects developed significantly elevated liver enzymes, (one also exhibited elevated bilirubin) considered possibly /probably related to CAB exposure. All three subjects were required to immediately discontinue study drugs per protocol liver stopping criteria and the transaminases subsequently returned to pre-treatment levels. Peak ALT elevations in these subjects was >10xULN and occurred from 4 to 8 weeks, after initiating daily oral CAB. None of the subjects had measurable change in hepatic function and all were largely asymptomatic. All three subjects had underlying hepatic disease (steatohepatitis n=2; chronic Hepatitis C with fibrosis n=1). There have been no Grade 3 or 4 ALT elevations in studies in which CAB LA has been administered to healthy volunteers (n=136) or as PrEP. Transient transaminase elevations (Grades 1 and 2) have been reported in subjects in Phase 2 studies, which have resolved on continued treatment.	Liver transaminases will be closely monitored throughout this study (refer to Time & Events Table Section 7.1) and Liver chemistry stopping criteria as outlined in Section 5.4.1 will be implemented as needed. All instances of liver transaminase elevations of Grade 2 and above will be followed to resolution. This risk will also be mitigated by enrolling healthy volunteers with normal liver chemistries as outlined by the exclusion criteria described in Section 5.2.
Injection Site Reactions (ISRs)	The occurrence of ISRs was identified in rats and monkeys at all dose levels of CAB LA and associated with both the IM and SC route of administration. In humans, experience to date has demonstrated that ISRs occur in the majority of exposed subjects but are generally mild (Grade 1) and include tenderness, erythema, or nodule formation of several days duration. Reactions to date have been mostly well tolerated. Two subjects have withdrawn from study due to ISRs. One subject in 201120 (ECLAIR) developed injection site pain, fever and myalgias after IM dosing with cabotegravir LA and withdrew from the study. Another subject in the maintenance phase of 200056 (HIV-1 treatment study) developed grade 2 injection site, pain, erythema and swelling with mild fevers after an IM dose of cabotegravir LA, and also withdrew from the study.	Subjects will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. Specialist dermatology consultation will be sought if warranted

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		for individual subjects.
Creatinine Phosphokinase (CPK) elevations	Occurrences of transient instances of elevations of CPK levels have been observed in Phase 1 studies and ongoing Phase 2 studies with CAB at dose levels of 10, 30 and 60 mg (LAI116482, 200056, 201120). These generally appeared to be related to physical activity, were not associated with clinical symptoms and returned to pre-treatment levels in the majority of cases. No subject has required a discontinuation of oral CAB as a result of a CPK elevation to date. However 3 subjects in the ongoing PrEP study (201120) were not transitioned to injectable drug as a precautionary measure having developed elevations in CPK. No reports of rhabdomyolysis have been received.	Standard laboratory monitoring as detailed in Section 7.4.6.
Bone marrow depletion	This risk was demonstrated in a high dose (1000 mg/kg/day) CAB monkey study but was not apparent from studies conducted in rats or at lower dose levels in monkeys. Signal not confirmed by human data to date. There have been isolated reports of transient neutropenia (maximum Grade 3) in subjects participating in an ongoing PrEP study but this generally normalised on continued treatment, was asymptomatic and appeared to represent routine fluctuations in subject's background blood picture.	The dose used within this study will result in many fold lower level exposure compared to the effect level in primates. Careful monitoring of adverse hematological events (including laboratory monitoring as in Section 7.4.6) will occur during study conduct. Serious/severe events will be managed appropriately with supportive care, and will be followed to resolution as per Sponsor's standard medical monitoring practices.
Gastrointestinal intolerability	The risk identified in a monkey toxicity study at the highest administered dose of CAB and considered related to local irritation (rather than a systemic effect) leading to morbidity associated with clinical signs of intolerance. In human subjects the frequency of GI events (nausea, vomiting, gastroenteritis, dyspepsia) has been similar to active comparators. No subjects have withdrawn due to drug related GI events to date.	Careful monitoring of adverse GI events will occur throughout the study. Serious/severe events will be managed appropriately with supportive care, and will be followed to resolution as per Sponsor's standard medical monitoring practices.

REVISED TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK1265744/Cabotegravir		
Elevated liver transaminases	As of October 1, 2015, 1153 subjects have been exposed to CAB (oral and/or long-acting injection) in phase 1 and 2 studies. Seventeen subjects have met protocol-defined liver stopping criteria, after having received cabotegravir over at least four weeks, of which five are considered to represent possible or probable cases of drug-induced liver injury.. None of these subjects developed clinical symptoms of liver dysfunction, and transaminases returned to pre-treatment levels after stopping drug.	Liver transaminases will be closely monitored throughout this study (refer to Time & Events Table Section 7.1) and Liver chemistry stopping criteria as outlined in Section 5.4.1 will be implemented as needed. All instances of liver transaminase elevations of Grade 2 and above will be followed to resolution. This risk will also be mitigated by enrolling healthy volunteers with normal liver chemistries as outlined by the exclusion criteria described in Section 5.2.
Injection Site Reactions (ISRs)	ISRs associated with CAB LA injection were very common, occurring in 74% of IM-exposed subjects, but generally were mild. The most frequent ISRs were pain, erythema and nodules. Median IM ISR duration was 7 days for pain and erythema and approximately 22 days for nodules.	Subjects will be closely monitored for ISRs particularly for signs of pain, tenderness, infections, erythema, swelling, induration, or nodules (granulomas or cysts) throughout the study. Specialist dermatology consultation will be sought if warranted for individual subjects.
Creatinine Phosphokinase (CPK) elevations	Occurrences of transient elevations of CPK levels have been observed in Phase 1 studies and ongoing Phase 2 studies with CAB at dose levels of 10, 30 and 60 mg (LAI116482, 200056, 201120). These generally appeared to be related to physical activity, were not associated with clinical symptoms and returned to pre-treatment levels in the majority of cases. Rhabdomyolysis of uncertain cause has been included in labelling for a currently available integrase inhibitor (raltegravir) but has not been seen in any subject receiving CAB to date.	Standard laboratory monitoring as detailed in Section 7.4.6.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Bone marrow depletion	This risk was demonstrated in a high dose (1000 mg/kg/day) CAB monkey study but was not apparent from studies conducted in rats or at lower dose levels in monkeys. Signal not confirmed by human data to date. There have been isolated reports of transient neutropenia (maximum Grade 3) in subjects participating in an ongoing PrEP study but this generally normalised on continued treatment, was asymptomatic and appeared to represent routine fluctuations in subject's background blood picture.	The dose used within this study will result in many fold lower level exposure compared to the effect level in primates. Careful monitoring of adverse hematological events (including laboratory monitoring as in Section 7.4.6) will occur during study conduct. Serious/severe events will be managed appropriately with supportive care, and will be followed to resolution as per Sponsor's standard medical monitoring practices.
Gastrointestinal intolerability	This risk was identified in a monkey toxicity study at the highest administered dose of CAB and considered related to local irritation (rather than a systemic effect) leading to morbidity associated with clinical signs of intolerance. Diarrhea, abdominal pain and vomiting have been observed in clinical studies but are generally well tolerated with few withdrawals.	Careful monitoring of adverse GI events will occur throughout the study. Serious/severe events will be managed appropriately with supportive care, and will be followed to resolution as per Sponsor's standard medical monitoring practices.

Section 5.2 Exclusion Criteria

ADDED TEXT

8. History of ongoing or clinically relevant seizure disorder within the previous 2 years, including subjects who have required treatment for seizures within this time period. A prior history of seizure, with a seizure free period of at least 2 years, off anti-epileptics, may be considered for enrolment if the investigator believes the risk of seizure recurrence is low. All cases of prior seizure history should be discussed with the medical monitor prior to enrolment.

Section 7 Study Assessments and Procedures

ADDED TEXT

- Allowable time windows for study assessments can be found in the SRM.

Section 7.5.1 Sample Analysis

PREVIOUS TEXT

Plasma/tissue/luminal fluid analysis will be performed under the control of the Clinical Pharmacology Analytical Laboratory (CPAL) at Johns Hopkins University. The details of sample collection and analysis will be included in the Procedures Manual and SOPs. Concentrations of CAB will be determined in samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

Assays are validated following FDA guidelines and approved by an NIH-cross network Clinical Pharmacology Quality Assurance (CPQA) program before used in clinical studies.

REVISED TEXT

Plasma/tissue/luminal fluid analysis will be performed by the Clinical Pharmacology Analytical Laboratory (CPAL) at Johns Hopkins University and under the management of GSK DMPK. The details of sample collection and analysis will be included in the SPM and additionally in the study sample analysis plan. Concentrations of CAB will be determined in samples using the currently approved bioanalytical methodology. Raw data will be stored at the bioanalytical site. At the end of the study, a copy of the raw data will be sent to GSK.

Validation testing will be performed in accordance with the FDA Bioanalytical Method Validation Guidance for Industry and assays reviewed in accordance with the NIH-cross network Clinical Pharmacology Quality Assurance (CPQA) program.

Section 10.6 Records Retention

ADDED TEXT

- A copy of all bioanalytical records will be returned to GSK at the conclusion of the study.