TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	Phase I, single-center, open label, fixed-sequence cross-over study to evaluate the effect of rifabutin on the pharmacokinetics of oral cabotegravir in healthy subjects

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N269788_00	2017-FEB-23	Original
2016N269788_01	2017-APR-13	Amendment No. 1
The purpose of this protocol amendment is to update Appendix 12.5.1." Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)" The updates include clarifying true abstinence for this study and the deletion of double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent foam/gel/film/cream/suppository) as a highly effective method for avoiding pregnancy in females of reproductive potential (FRP) .		
2016N269788_02	2017-JUN-29	Amendment No. 2
The purpose of this protocol amendment is to: Clarify the required days for fasting (Day 14 and Day 28). Remove Appendix 12.4.3- Definition of Cardiovascular Events. The collection of Cardiovascular Events is not applicable to the 205712 study.		

SPONSOR SIGNATORY

PPD

4/29/17

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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): 109,678

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205712 Amendment 2

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 205712

Rationale

Cabotegravir (CAB) is a 2-metal binding integrase inhibitor being developed for the treatment and prevention of HIV-1 infection as both an oral and long acting (LA) injectable nanosuspension. Rifabutin (RBT) is an antimycobacterial agent used for the treatment of tuberculosis as well as for both treatment and prevention of *Mycobacterium avium intracellulare* (MAC) in advanced HIV infection in individuals with low CD4 cell counts. RBT is chemically related to rifampin (RIF), the latter is a potent inducer of UDP (Uridine 5'-diphospho-glucuronosyltransferase) -glucuronosyltransferases (UGTs) and Cytochrome P450 3A4 (CYP3A4). RBT appears to induce P450 enzymes and UGTs as well, although not as potently as RIF. CAB is primarily metabolized via UGT1A1 and UGT1A9. Evidence from the human mass balance and related metabolite identification studies suggests that the CYP enzyme involvement in the metabolism of CAB is likely to be minimal. Given that RBT is considered to be a weak enzyme inducer, it is anticipated that RBT will modestly reduce CAB exposures during concomitant administration. This study is being conducted to evaluate the drug-drug interaction (DDI) potential between CAB and RBT to inform dosing strategies for tuberculosis in subjects receiving CAB for HIV treatment or prevention.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To compare steady state CAB exposure following 30 mg oral dose once daily with and without RBT 300 mg once daily	• Plasma CAB AUC(0-τ), Cmax
Secondary	
• To describe the pharmacokinetic (PK) of CAB 30 mg oral dose once daily administered alone and with RBT	• Plasma CAB Cτ, tmax, t1/2, CL/F
• To assess the safety and tolerability of CAB 30 mg oral dose alone and in combination with RBT 300 mg oral dose once daily	• Safety and tolerability parameters, including adverse events, concurrent medication, clinical laboratory screens, electrocardiogram (ECG), and vital signs assessments.

$AUC_{(0-t)}$ = area under the plasma concentration time curve from time zero to the last quantifiable time point
C_{max} = maximum observed concentration
Ct = last quantifiable concentration
t_{max} = time of maximum observed concentration
$t_{1/2}$ = the elimination half-life
- CL/F = apparent oral clearance

Overall Design

This is a Phase I, single-center, open-label, fixed-sequence, 2-period crossover study in healthy adults to evaluate the effect of RBT on the PK of oral CAB 30 mg.

Study Design

Subjects	Screening Period	Period 1 Days 1 – 14	Period 2 Days 15 - 28	Follow-up
N=15	Within 30 Days of Day 1	Treatment A: once daily x 14 days	Treatment B: once daily x 14 days	~10-14 days after last dose of CAB

- Treatment A = CAB 30 mg once daily x 14 days
- Treatment B = RBT 300 mg once daily + CAB 30 mg once daily x 14 days

Treatment Periods and Duration

This study will take place in two treatment periods and a follow-up period. All subjects will undergo a screening visit within 30 days from the first dose of study drug. The overall study duration will be approximately 10 weeks (4 weeks screening, 2 weeks for treatment Period 1, 2 weeks for treatment Period 2, and 2 week follow-up period).

Treatment Period 1: Treatment A: CAB 30 mg once daily x 14 days

Treatment Period 2: Treatment B: RBT 300 mg once daily + CAB 30 mg once daily x 14 days

Type and Number of Subjects

- Approximately 15 healthy adult subjects will be enrolled to ensure that 12 subjects will complete dosing and critical assessments.

- If subjects prematurely discontinue the study, additional replacement subjects may be enrolled and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

Analysis

No formal hypothesis will be tested. An estimation approach will be used to evaluate the effect of RBT on CAB PK parameters. Point estimates and corresponding 90% confidence intervals (CIs) will be constructed for the comparisons of interest (test:reference).

2. INTRODUCTION

2.1. Study Rationale

Cabotegravir (CAB) is a 2-metal binding integrase inhibitor being developed for the treatment and prevention of Human immunodeficiency virus-1 (HIV-1) infection as both an oral and long acting (LA) injectable nanosuspension.

Tuberculosis (TB)/HIV co-infection is common and both conditions often need to be treated simultaneously. RIF is a backbone component of TB treatment regimens and is a potent inducer of UDP-glucuronosyltransferases (UGTs) and Cytochrome P450 3A4 (CYP3A4). CAB is primarily metabolized via UGT1A1 and UGT1A9. Evidence from the human mass balance and related metabolite identification studies suggests that the CYP enzyme involvement in the metabolism of CAB is likely to be minimal. A reduction in CAB serum concentrations due to drug-drug interaction with RIF could lead to a risk of treatment failure and the emergence of HIV drug resistance. RIF increased CAB oral clearance 2.4-fold and reduced CAB AUC(0- τ)) and terminal phase t1/2 by 59% and 57%, respectively. RIF had no effect on CAB Cmax. Therefore, co-administration of RIF with oral CAB 30mg once daily is not recommended [Ford, 2016].

RBT is an alternative anti-mycobacterial agent used for the treatment of tuberculosis. RBT is chemically related to RIF and is considered a weaker enzyme inducer of UGTs and CYP3A as compared to RIF. The effect of RBT on the PK of CAB has not been studied to date. Raltegravir (RAL) is an integrase inhibitor that is also primarily metabolized via UGT1A1. RAL area under the concentration-time curve over 12 hours (AUC[0-12]) increased by 19% while minimum observed concentration (Cmin) decreased by 20% during concurrent RBT administration [Brainard, 2011]. Dolutegravir (DTG), another marketed HIV integrase inhibitor, is primarily metabolized via UGT1A1 with a minor CYP3A component. Following co-administration of DTG 50 mg once daily with RBT 300 mg once daily, DTG AUC(0-τ) was unchanged [GMR (90% CI) 0.95 (0.82, 1.10)], Cmax was increased 15% [GMR (90% CI) 1.15 (0.97 ,1.36)], and Cτ was decreased 30% [GMR (90% CI) 0.70 (0.57 ,0.87)], [GlaxoSmithKline Document Number RM2008/00856/00 ITZ111839 ; Ford, 2013]. Based on RBT drug-drug interaction (DDI) data with RAL and DTG, a significant DDI between CAB and RBT is not expected. Because CAB does not induce or inhibit RBT metabolizing enzymes, the impact of CAB on RBT PK will not be evaluated in this study.

This DDI study will evaluate the impact of RBT on the pharmacokinetics of CAB. The results of this study will inform dosing strategies for the management of tuberculosis in patients receiving CAB for HIV treatment or prevention

2.2. Brief Background

Tuberculosis (TB) is surpassed only by human immunodeficiency virus (HIV) as a cause of infectious disease-associated deaths worldwide [Frieden, 2003]. In 2012, 1.1 million of an estimated 8.6 million people who developed TB worldwide were HIV-positive [World Health Organization, 2014]. Given that the yearly incidence of TB is 10% in HIV-infected individuals, concomitant treatment for TB is common [Maartens, 2007].

Increasingly, the two diseases will be treated concurrently in co-infected individuals. Two recent studies evaluating the optimal timing for initiation of highly active antiretroviral therapy (HAART) in subjects requiring treatment for active TB demonstrated a survival benefit for treating HIV during TB treatment rather than waiting until after TB treatment completion [Abdool, 2010a; Abdool, 2010b]. However, co-treatment is complex and difficult owing to drug-drug interactions, immune reconstitution inflammatory syndrome, and overlapping toxicities [McIlleron, 2007].

Although TB is a global issue, the geographic distribution of cases is drastically disproportionate. The spread of HIV and multidrug resistance has fuelled the TB epidemic, and in less-developed countries, TB is the most common cause of death in HIV-infected patients [Corbett, 2003]. Ninety-five percent of all TB cases and 98% of all TB deaths occur in developing countries. Only 22 high-burden countries (HBCs) account for 80% of the global TB burden, with half of these countries located within Asia. In Africa, 40 countries have an estimated TB prevalence rate greater than 100/100,000 compared to the estimated prevalence rate of <5/100,000 in the United States [U.S. Department of Health and Human Services, 2014].

Currently, rifamycins serve as the cornerstone of TB therapy because of their unique sterilizing activity. RIF (rifampicin), the most commonly-used rifamycin, is a semi-synthetic rifamycin derivative that is highly active against mycobacteria, most gram-positive bacteria, and some gram-negative bacteria. It is bactericidal for both intracellular and extracellular microorganisms. By inhibiting prokaryotic deoxyribonucleic acid (DNA) -dependent ribonucleic acid (RNA) polymerase, it suppresses the early elongation of the nucleotide chain in RNA synthesis. RIF is a potent inducer of a number of hepatic enzymes involved in the metabolism of drugs and some hormones, including UGTs and CYP450 enzymes [Venkatesan, 1992]. Significant enzyme induction from RIF limits concurrent use with many antiretroviral agents, therefore RBT may be an alternative due to its weak enzyme induction potential. Most antiretrovirals can be co-administered with RBT without dose adjustment, including the integrase inhibitors, raltegravir and dolutegravir, however, enzyme induction or inhibition by non-nucleoside reverse transcriptase inhibitors and boosted protease inhibitors, require dose modification of RBT in some cases [Yapa, 2016].

As of October 18 2016, the efficacy, safety, and PK of CAB have been evaluated in 19 (15 completed, 2 concluded and 2 ongoing) Phase I/IIa ViiV sponsored clinical trials with oral CAB and CAB LA. Subjects have been exposed to single oral doses of CAB ranging from 5-150 mg and repeat once daily doses of 30 mg for 10-28 days in duration. There have been no deaths or drug-related SAEs. There were no clinically significant trends in lab events, ECG, or vital sign changes, or QTcF >500 msec or QTcF change from baseline >60 msec. Refer to the Investigators Brochure (IB) for additional information.

3. OBJECTIVES AND ENDPOINTS

Primary	
• To compare steady state CAB exposure following 30 mg oral dose once daily with and without RBT 300 mg once daily.	• Plasma CAB_AUC(0-τ), Cmax
Secondary	
• To describe the pharmacokinetic (PK) of CAB 30 mg oral dose once daily administered alone and co-administered with RBT.	• Plasma CAB_Cτ, tmax, t1/2, CL/F
• To assess the safety and tolerability of CAB 30 mg oral dose administered alone and in combination with RBT 300 mg once daily.	• Safety and tolerability parameters, including adverse events, concurrent medication, clinical laboratory screens, electrocardiogram (ECG), and vital signs assessments.
$AUC_{(0-t)}$ = area under the plasma concentration time curve from time zero to the last quantifiable time point C_{max} = maximum observed concentration Ct = last quantifiable concentration t_{max} = time of maximum observed concentration $t_{1/2}$ = the elimination half-life • CL/F = apparent oral clearance	

4. STUDY DESIGN

4.1. Overall Design

This study is a phase I, single-center, open label, fixed-sequence, 2-period crossover study in healthy adults to evaluate the effect of RBT on the PK of oral CAB 30 mg.

Table 1 Study Design

Subjects	Screening Period	Period 1 Days 1 – 14	Period 2 Days 15 - 28	Follow-up
N=15	Within 30 Days of Day 1	Treatment A	Treatment B	~10-14 days after last dose of CAB
• Treatment A = CAB 30 mg once daily x 14 days • Treatment B = RBT 300 mg once daily + CAB 30 mg once daily x 14 days				

4.2. Treatment Periods and Duration

Subjects will undergo a screening visit within 30 days of the first dose of study drug, followed by two treatment periods and a follow-up period.

Subjects will undergo clinical safety assessments and serial PK assessments at time-points specified in Section 7.1, Time and Events table of the protocol.

Period 1

Eligible participants will be admitted to the unit on Day -1.

On Day 1, following completion of the required pre-dose measurements, the investigator or authorized study unit personnel will administer a single oral dose of 30 mg CAB to each subject in the unit.

Subjects will be dispensed a bottle of CAB to be taken at home on Days 2-12 and discharged from the unit. Subjects will be provided with a subject diary to document daily recordings of dosing occurring outside of the unit. Subjects will be re-admitted to the unit in the morning on Day 13. Prior to dosing, a CAB PK sample will be obtained, and then the subjects will receive a single 30 mg dose of CAB on Day 13 and remain in the unit overnight. On Day 14, following an overnight fast of at least 6 hours, subjects will receive a single 30 mg dose of CAB with serial CAB PK samples collected pre-dose and through 24 hours after dosing up to Day 15. There will be no washout between Period 1 and Period 2.

Period 2

On Day 15 following the completion of the required Day 14 safety assessments and PK collection, subjects will proceed to Period 2, where site staff will administer a single dose of RBT 300 mg and a single dose of CAB 30 mg in the unit. Subjects will be discharged and dispensed a bottle of RBT and a bottle of CAB to be taken at home on Days 16-20. Subjects will be provided with a subject diary to document daily recordings of home dosing. In the morning of Day 21, subjects will bring their bottle of RBT and bottle of CAB for observed dosing in the unit and safety assessments as an outpatient visit. Following these procedures, subjects will be discharged with their supply of CAB and RBT and instructed to take their daily doses of study medications at home in the mornings of Days 22 through 25. On Day 26, subjects will return to the unit for a pre-dose PK collection and observed dosing as an outpatient visit and then be discharged home. On Day 27, subjects will be re-admitted to the unit for a pre-dose PK collection, observed dosing, and safety assessments then remain in the unit overnight. In the morning of Day 28 following an overnight fast of at least 6 hours, subjects will receive a single dose of RBT and a single dose of CAB in the unit with serial CAB PK samples collected pre-dose and through 24 hours after dosing up to Day 29. Subjects will be discharged from the unit on Day 29 after the final assessment is completed. Subjects will complete a follow-up visit ~ 10-14 days after the last 30 mg oral dose of CAB.

At the follow-up visit, laboratory safety assessments (including pregnancy test for females of childbearing potential) will be performed, and vital signs together with a 12-lead ECG will be obtained.

4.3. Type and Number of Subjects

- Approximately 15 healthy adult subjects will be enrolled to ensure that 12 subjects will complete dosing and critical assessments.

- If subjects prematurely discontinue the study, additional replacement subjects may be allocated and assigned to the same treatment sequence (A then B) at the discretion of the Sponsor in consultation with the investigator.

4.4. Design Justification

This open-label, fixed sequence, cross-over design is well-established for evaluation of drug-drug interaction potential of a perpetrator drug (e.g., RBT) to affect the pharmacokinetics of a victim drug (e.g., CAB). Conducting the study in a fixed sequence with daily administration of CAB 30 mg/day for 14 days and then assessing CAB PK over 24 hours after the Day 14 dose of CAB will enable characterization of CAB PK by itself. This will avoid the possibility for any inductive effect caused by RBT dosing prior to oral administration of CAB alone, as would be the case if the study treatments were to be randomized. Then, in the second treatment period, oral co-administration of RBT 300 mg once daily and CAB 30 mg once daily for 14 days with the assessment of CAB PK over 24 hours after the Day 28 dosing of CAB and RBT will facilitate assessment of CAB PK in the presence of RBT at steady-state to observe the likely maximum inductive impact of RBT.

The study is subject to the appropriate regulatory approval and Ethics Committee approval, 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

A CAB 30 mg single dose was selected for this study as it is the oral induction dose that is currently under investigation in the ongoing Phase 2b treatment studies [Protocols GlaxoSmithKline Document Number 2012N134026_01, GlaxoSmithKline Document Number 2013N168152_04, 200056] and is the oral induction dose taken into the Phase 3 studies (the FLAIR and ATLAS studies). Additionally, for PrEP studies in healthy, uninfected subjects, the 30 mg oral dose has been selected for oral lead-in therapy prior to injectable dosing in the completed ECLAIR study [Protocol GlaxoSmithKline Document Number 2013N184048_01, 201120 and the DAIDS Document ID: 11964 HPTN 077, 2014 . In two oral relative bioavailability studies [GlaxoSmithKline Document Number 2012N136689_00, LAI116585 and GlaxoSmithKline Document Number 2013N165475_00, LAI117020], CAB AUC(0-∞) was well-estimated with 168 hrs of sampling following single dose CAB 30 mg (sodium salt tablet formulation). For these two studies, geometric mean AUC(0-∞) values were 174µg*h/mL and 141µg*h/mL, and Cmax values were 4.24 µg/mL and 3.70 µg/mL. Assuming a maximal induction effect by

RBT of 70-80% reduction, CAB exposure may approximate that of a 5-10 mg oral dose, the PK for which has also been well-characterized following single dose administration.

RBT 300 mg once daily was selected for this study not only for its role as an alternative rifamycin for anti-tuberculosis therapy but also because it is the recommended dose for as it is the recommended dose for the prevention of disseminated Mycobacterium avium complex (MAC) in patients with advanced HIV infection (CD4+ cell count <200/mm3 with an AIDS defining diagnosis, or CD4+ cell count <100/mm3 without an AIDS defining diagnosis). The terminal half-life of RBT is approximately 38 hours. Enzyme induction by RBT has been demonstrated to occur within 7 days of therapy and auto-induction of its own metabolism has been demonstrated to occur within 10 days in healthy volunteers [Perruca, 1988]. RBT 300 mg (two 150 mg capsules) once daily will be administered for 14 days with CAB 30 mg (one 30 mg tablet) once daily for 14 days in Treatment Period 2 to ensure that the maximal inductive effect of RBT is achieved.

The duration of dosing in this study was chosen partly based on scientific convention with similar P1 drug-drug interaction studies and particular to this protocol, because of the importance of achieving a steady state concentration of study drug (CAB) before PK analyses of CAB are performed during Period 1 of the study. Similarly, in Period 2 of the study, a similar rationale for duration of 14 days applies to the combination of CAB and RBT as well. Oral CAB has a terminal phase elimination t½ of approximately 40 hours and reaches steady state by 10-12 days of once daily administration, supporting 14 days of dosing in this study [GlaxoSmithKline Document Number 2012N136689_00, LAI116585]. Before obtaining PK assessments, both CAB and RBT need to reach steady state and 14 days is sufficient time for that to occur.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK1265744 (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-Cabotegravir

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) Cabotegravir		
Drug Induced Liver Injury (DILI)	A small proportion of participants in the CAB program to date (total exposure approximately 1289 as of 01 October 2016) have developed transaminitis (elevated liver transaminases characterised by predominant alanine aminotransferase [ALT] elevation). In some of these participants, transient transaminitis was explained by acute hepatitis C infection whilst a small number of others did not have alternative explanations, suggesting a mild form of DILI without hepatic dysfunction which resolved upon withdrawal of treatment with CAB. Of the five participants with possible or probable cases of DILI identified in Phase 2 studies, four participants were receiving oral CAB and one participant developed probable DILI following CAB LA or Placebo LA administration.	• Exclusion criteria as described in Section 5.2 will prohibit participants with significant liver impairment based on prior medical history and screening liver chemistry including transaminases (ALT and Aspartate aminotransferase [AST]). • 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 5.4.2 of this protocol. • All instances of liver transaminase elevations of Grade 2 and above will be followed to resolution. Participants withdrawn from CAB treatment due to meeting liver chemistry stopping criteria will be regularly monitored both clinically and using liver chemistries to determine progress towards resolution of the liver event.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) Cabotegravir		
Hypersensitivity Reactions (HSR)	Hypersensitivity reactions have been reported as uncommon occurrences with integrase inhibitors, including the closely related compound dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. While there have been no clinical cases of hypersensitivity to CAB, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic symptoms.	• 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. Any HSR reactions that occur would be managed supportively.

4.6.2. Risk Assessment-Rifabutin

Adverse reactions identified through post-marketing surveillance by system organ class (SOC) include: blood cell disorders (agranulocytosis, lymphopenia, granulocytopenia, neutropenia, leukopenia, and thrombocytopenia), immune system disorders (hypersensitivity, bronchospasm, rash, and eosinophilia), and gastrointestinal disorders (*Clostridium difficile* colitis/ *Clostridium difficile* associated diarrhea). Pyrexia, rash and other hypersensitivity reactions such as eosinophilia and bronchospasm might occur, as has been seen with other anti-bacterials. A limited number of skin discolorations have been reported. Hypersensitivity to rifamycins has been reported including flu-like symptoms, bronchospasm, hypotension, urticaria, angioedema, conjunctivitis, thrombocytopenia or neutropenia. See below for the Rifabutin risk assessment and mitigation strategy for this protocol.

Neutropenia: Neutropenia is commonly experienced in patients receiving RBT and rapidly resolves with discontinuation of RBT. Subjects will have frequent hematology laboratory monitoring and the neutropenia stopping rule is in place, see Section 5.4.4.

Uveitis: Subjects will be followed for development of ocular AEs since RBT has been associated with this complication, although it is rare when administered as 300 mg/day. Uveitis can develop from 2 weeks to more than 7 months after initiation of RBT treatment [Tseng, 1995]. Discontinuation of RBT or dose reduction generally results in resolution of uveitis and complete recovery of visual acuity is typical with drug withdrawal and topical treatment. Subjects with evidence of new ocular symptoms consistent with uveitis (eye pain, eye redness, light sensitivity, blurriness or change in vision, that is not attributed to allergic, infectious (bilateral viral/bacterial conjunctivitis or HSV keratitis), acute angle-closure glaucoma, corneal abrasions, scleritis, or secondary to trauma including intraocular foreign body will be discontinued from study treatment, and referred to ophthalmology for evaluation and appropriate treatment. Refer to Ocular stopping criteria, Section 5.4.1

Hypersensitivity Reaction (HSR): Clinical assessments, laboratory tests (including liver transaminases) and vital signs assessments will be performed throughout this study (refer to Time & Events Table). Results from these assessments may aid early detection of HSR. RBT will be withdrawn immediately for cases with suspected HSR. Any HSRs that occur would be managed supportively.

Risk Assessment- Rifabutin

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Neutropenia	Neutropenia is commonly experienced in patients reeiving RBT and rapidly resolves with discontinuation of RBT	• Subjects in protocol 205712 will have frequent hematology laboratory monitoring and a neutropenia stopping rule is in place, see Section 5.4.4

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Uveitis	While RBT can cause uveitis, the condition occurs more often with higher doses than what is being evaluated in this study (300 mg).	• While the likelihood of uveitis is low with the dose used in 205712, patients with a current of past history of uveitis will be excluded from this study (exclusion criteria #7). Also, a uveitis stopping criteria (Section 5.4.1) has been added to the protocol and subjects who develop eye pain, eye redness, blurry vision or photosensitivity not attributed to allergic, infectious (bilateral viral/bacterial conjunctivitis or HSV keratitis), acute angle-closure glaucoma, corneal abrasions, scleritis, or secondary to trauma (including intraocular foreign body) will be discontinued from study treatment, and referred to ophthalmology for evaluation and appropriate treatment. Medical monitor will be notified if a patient develops any signs or symptoms of acute uveitis as noted above.
Hypersensitivity Reaction (HSR)	While not commonly described, HSR can occur with the administration of any medicinal product including RBT	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. RBT will be withdrawn immediately for cases with suspected HSR. Any HSR reactions that occur would be managed supportively.

For risks associated with trade name, please refer to the Summary of Product Characteristics (SmPC) [Summary of Product Characteristics for Mycobutin, January 2016]**.**SmPC will serve as the reference safety information for Mycobutin.

4.6.3. 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 programme cumulatively through 01 October 2016. Two of the cases occurred in HIV uninfected subjects with a prior history of seizure and one case involved a subject in study 200056 [GlaxoSmithKline Document Number 2013N168152_04, 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.

4.6.4. Benefit Assessment

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

4.6.5. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with CAB and RBT are justified by the anticipated benefits that may be afforded to subjects with HIV and to those healthy subjects who may benefit from CAB as a preventative agent for acquisition of HIV.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GlaxoSmithKline (GSK) investigational product or other study treatment that may impact subject *eligibility* is provided in the IB for cabotegravir (CAB) and the Product Monograph for Mycobutin Capsules (rifabutin capsules).

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

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 Investigators Brochure (IB).

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

AGE
1. Males and females between 18 and 65 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. Additionally, laboratory assessments that are specifically listed in the inclusion or exclusion criteria and are outside of the reference range can be repeated once during the screening period.

WEIGHT
4. Body weight ≥50 kg and body mass index (BMI) within the range 18.5 – 31.0 kg/m2 (inclusive).

SEX
5. Male or female A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal with one of the following: • Documented tubal ligation • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion • Hysterectomy • Documented Bilateral Oophorectomy • Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause FSH: >40 MIU/mL and estradiol <40 pg/mL (<147 pmol/L) is confirmatory]. b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy

Information) from 30 days prior to the first dose of study medication until the completion of the follow-up visit.

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

INFORMED CONSENT

6. 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.

ACCEPTABLE LIVER CHEMISTRY AND HEMATOLOGY CRITERIA

7. ALT, alkaline phosphatase and bilirubin ≤1xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
8. White blood cell count and absolute neutrophil count in the normal range.

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)

1. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
2. History of clinically significant cardiovascular disease including:
    a. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart rate	<45 and >100 beats per minute	<50 and >100 beats per minute
QRS duration	>120 msec	
QTc interval (F)	>450 msec	

    b. Evidence of previous myocardial infarction (pathologic Q waves, S-T segment changes (except early repolarization).
    c. 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.
    d. 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) which in the opinion of the principal Investigator and Viiv Medical Monitor, will interfere with the safety for the individual subject.

e. Sinus pauses >3 seconds.

f. Any significant arrhythmia which, in the opinion of the principal Investigator and ViiV Medical Monitor, will interfere with the safety for the individual subject.

g. Non-sustained (≥3 consecutive ventricular ectopic beats) or sustained ventricular tachycardia.

NOTES:

- The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), machine-read or manually over-read.

3. History of inflammatory bowel disease.
4. History of cholecystectomy or other gastrointestinal surgery (except appendectomy more than three months prior to study).
5. History of peptic ulceration or pancreatitis within the preceding 6 months of screening.
6. Participants determined by the Investigator to have a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder. A participant with a prior history of seizure may be considered for enrolment if the Investigator believes the risk of seizure recurrence is low. All cases of prior seizure history should be discussed with the Medical Monitor prior to enrolment.
7. Current or past history of uveitis.
8. Any other medical condition which, in the judgment of the investigator and medical monitor, could jeopardize the safety of the subject or the integrity of the data derived from that subject. This includes but is not limited to any pre-existing condition that interferes with normal gastrointestinal anatomy or motility that could interfere with the absorption, metabolism, and/or excretion of the study drug.

CONCOMITANT MEDICATIONS

9. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and Viiv Medical Monitor the medication will not interfere with the study procedures or compromise subject safety. See Section 6.10.2 for concomitant medications that are prohibited for this study.

RELEVANT HABITS

10. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >14 drinks. 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. A history of regular use of tobacco, or nicotine-containing products within 30 days prior to screening.

CONTRAINDICATIONS
12. 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.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
13. Presence of Hepatitis B surface antigen (HBsAg) positivity at screening or within 3 months prior to first dose of study treatment. Positive Hepatitis B core antibody (HBcAb) with negative hepatitis B surface antibody should also be excluded. 14. Positive Hepatitis C antibody test. 15. A positive pre-study drug/alcohol screen. 16. A positive test for HIV antibody. 17. A positive QuantiFERON Gold test or clinical evidence of tuberculosis (TB) infection. 18. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period. 19. 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). 20. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

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 randomized. 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 Serious Adverse Events (see Section 7.3.1.4). Data for screen and baseline failures will be collected in source documentation at the site and will be transmitted to GSK.

5.4. Withdrawal/Stopping Criteria

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".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. 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 treatment phase, pre-specified reasons for discontinuing a participant from the study (or, discontinuing administration of study product and continuing safety evaluations) may include:

- Pregnancy (please see Section 7.3.2)
- Protocol deviation
- Non-compliance
- Subject withdraws consent
- Subject lost to follow-up
- Investigator discretion
- Sponsor discontinues study

5.4.1. Ocular Stopping Criteria

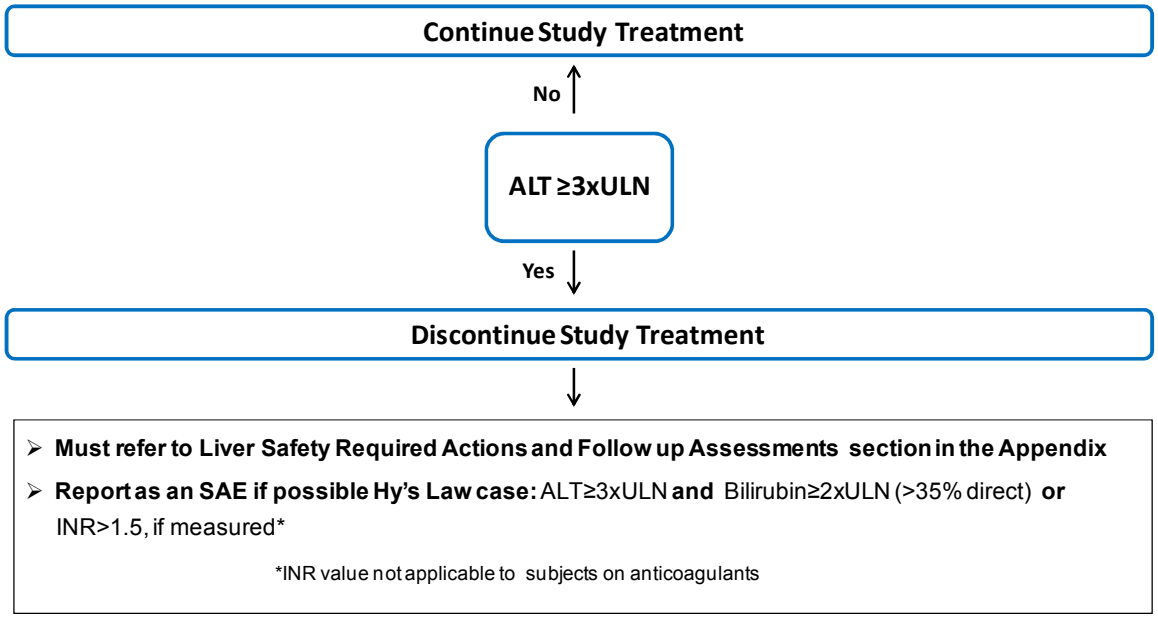
Subjects who develop eye pain, eye redness, blurry vision or photosensitivity not attributed to allergic or infectious (bilateral viral/bacterial conjunctivitis or HSV keratitis) causes, or to, acute angle-closure glaucoma, corneal abrasions, scleritis, or secondary to trauma (including intraocular foreign body) will be discontinued from study treatment, and referred to ophthalmology for evaluation and appropriate treatment. Medical monitor should be notified if a patient develops any signs or symptoms of acute uveitis as noted above.

5.4.2. Liver Chemistry Stopping Criteria

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). See Appendix 2 for details.
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:

Figure 1 Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

5.4.2.1. Study Treatment Restart or Rechallenge

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

Refer to Appendix 2 for full guidance.

5.4.3. QTc Stopping Criteria

- Fridericia's QT 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.

Fridericia's QT correction formula must continue to be used for that subject *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 period 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 either bulleted criterion below will be withdrawn from the study.

- QTcF> 500 msec,
- Change from baseline: QTc >60 msec

5.4.4. Neutropenia Stopping Criteria

Subjects with an absolute neutrophil count (ANC) less than 1 x10^9/L will be discontinued from study treatment. The presence of ANC less than 1 x10^9/L and a single measured temperature of >38.3 ºC or a sustained temperature of ≥ 38 ºC (100.4 ºF) for more than one hour refers to neutropenic fever and subjects should be referred for urgent evaluation and appropriate management.

5.4.5. Uveitis Stopping Criteria

Subjects who develop eye pain, eye redness, blurry vision or photosensitivity not attributed to allergic, infectious (bilateral viral/bacterial conjunctivitis or herpes simplex virus [HSV] keratitis), acute angle-closure glaucoma, corneal abrasions, scleritis, or secondary to trauma (including intraocular foreign body) will be discontinued from study treatment, and referred to ophthalmology for evaluation and appropriate treatment. Medical monitor should be notified if a patient develops any signs or symptoms of acute uveitis as noted above.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

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

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.

Table 2 Investigational Treatment and Other Study Treatment

	Study Treatment	
Product name:	**Cabotegravir Tablets, 30 mg**	**MYCOBUTIN Capsules (rifabutin capsules) sourced in the United Kingdom (UK)**
Formulation description:	GSK1265744B (micronized) lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, magnesium stearate, Aquarius film-coating, white BP18237	Rifabutin, microcrystalline cellulose, sodium lauryl sulphate, magnesium stearate, and silica gel. Rifabutin supplied as hard gelatin capsules having an opaque red-brown cap and body, each containing 150 mg of rifabutin.
Dosage form:	Tablet	Capsule
Unit dose strength(s)/Dosage level(s):	Tablet strength: 30 mg/Dose level: 30 mg	Capsule strength = 150 mg Dose level = 300 mg
Route of Administration:	Administer orally	Administer orally
Dosing instructions[1]:	Administer 1 tablet with 240 mL of water once daily	Administer 2 capsules with 240 mL of water once daily.
Manufacturer/Source of Procurement:	GlaxoSmithKline	Pfizer Limited Ramsgate Road Sandwich Kent CT139NJ United Kingdom
Method of individualizing dosage:	30 mg = one 30 mg tablet	300 mg = two 150 mg capsules
[1] Dosing of study medication on non-PK days may be with or without food, but dosing on serial PK days (Day 14 in Period 1 and Day 28 in Period 2) must be after an overnight fast of at least 6 hours, and no food will be allowed for 4 hours after dosing on these serial PK days.		

6.2. Treatment Assignment

In this study, following the 30 day screening period, subjects will be assigned to a single sequence in accordance with the single sequence schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Treatment Assignment for 205712

- Treatment A = CAB 30 mg once daily x 14 days
- Treatment B = RBT 300 mg once daily + CAB 30 mg once daily x 14 days

6.3. Blinding

This study is not blinded.

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

No special preparation of study treatment is required.

- 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 Study Reference Manual (SRM).
    - 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 site personnel will examine each subject's mouth to ensure that the study treatment was ingested.

When subjects self-administer study treatment(s) at home, compliance with CAB and RBT dosing will be assessed through verifying the diary entries and querying the subject during the site visits and documented in the source documents and case report form (CRF). A record of the number of CAB and RBT capsules dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will also be recorded in the CRF.

6.7. Treatment of Study Treatment Overdose

For this study, any dose of CAB >30 mg and RBT >300 mg within a 12 hour time period will be considered an overdose.

In the event of an overdose of RBT, and depending on the degree of overdose and investigator evaluation, gastric lavage and diuretic treatment should be carried out. Supportive care and symptomatic treatment should be administered [Summary of Product Characteristics for Mycobutin, January 2016].

GSK does not recommend specific treatment for an overdose of CAB.

In the event of an overdose the investigator should:

1. contact the Medical Monitor immediately
2. closely monitor the subject for AEs/ SAEs and laboratory abnormalities until CAB and RBT can no longer be detected systemically (at least 14 days for CAB)
3. obtain a plasma sample for pharmacokinetic (PK) analysis within 60 hours from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
4. document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

- Subjects must refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication until after the final PK sample.
- Dosing of study medication on non-PK days may be with or without food, but dosing on serial PK days (Day 14 in Period 1 and Day 28 in Period 2) must be after an overnight fast of at least 6 hours, and no food will be allowed for 4 hours after dosing on these serial PK days.

6.9.2. Caffeine, Alcohol, and Tobacco

- During each treatment period, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for

24 hours prior to the start of dosing until collection of the final PK sample of the study.

- During each treatment period, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final PK of the study.
- Use of tobacco products is not allowed from screening until after the final follow-up visit.

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 studies (e.g., watch television, read).

6.10. Concomitant Medications and Non-Drug Therapies

6.10.1. Permitted Medications and Non-Drug Therapies

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

6.10.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

Use of antacids, vitamins and iron supplements are strictly prohibited within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication and for the duration of the trial.

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.

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

- Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) 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/IEC 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.

7.1. Time and Events Table

Procedure	Screen[1]	Day -1	Treatment Period 1 Day														Treatment Period 2 Day																Early Withdrawal / Follow-up ~10-14 days
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21[2]	22	23	24	25	26[2]	27	28	29	
Informed consent	X																															
Inclusion and exclusion criteria	X	X																														
Demography	X																															
Full physical exam[3]	X																															
Brief physical exam[3]		X														X							X									X[4]
Medical/medication/drug/alcohol history	X	X														X							X									
Pregnancy test [5]	X	X														X														X			X
FSH and estradiol (if needed)	X																															
TB, HIV, Hep B, Hep C screen	X																															
Drug/Alcohol screen	X	X													X															X			
Safety Laboratory assessments	X	X													X								X							X			X
12-lead ECG[6]	X		X													X															X		X
Vital signs (Including Temperature)[6]	X		X													X							X							X			X

Procedure	**Screen**[1]	**Day -1**	**Treatment Period 1 Day**														**Treatment Period 2 Day**															**Early Withdrawal / Follow-up ~10-14 days**
			1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**[2]	**22**	**23**	**24**	**25**	**26**[2]	**27**	**28**	**29**	
Administer CAB 30 mg once daily[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Administer RBT 300 mg once daily[7]																	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense CAB[8]			X																													
Dispense CAB[9]and RBT[10]																	X															
Pharmacokinetic Sampling[11]															X	X-----X												X	X	X-----X		
Admit to Unit		X													X														X			
Discharge from Unit			X														X														X	
Outpatient Visit	X																						X					X				X
Drug accountability															X								X					X	X			
Genetic sample[12]			←==========→																													
SAE Review	←==========→																															
AE Review			←==========→																													
Concomitant medication review			←==========→																													

Procedure	Screen[1]	Day -1	Treatment Period 1 Day														Treatment Period 2 Day															Early Withdrawal / Follow-up ~10-14 days
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21[2]	22	23	24	25	26[2]	27	28	29	

1. Screening must be performed within 30 days prior to receiving the dose of CAB on Day 1.
2. Day 21 and Day 26 is an outpatient visit.
3. An ocular assessment will be performed only for subjects who experience eye symptoms.
4. A brief symptom directed physical exam will be completed as needed.
5. A serum pregnancy test will be performed at the screening visit and a urine pregnancy test at all other time points specified.
6. Duplicate ECG, BP, and HR assessments will be conducted pre-dose on Day 1. Single measurements will be collected at all other time points.
7. Study medication will be administered with 240 mL of water within the unit on Days 1, 13, 14, 15, 21, 26, 27, and 28. Dosing on non-PK days may be with or without food, but dosing on serial PK days (Day 14 in Period 1 and Day 28 in Period 2) must be after an overnight fast of at least 6 hours, and no food will be allowed for 4 hours after dosing on these serial PK days.
8. Dispense the bottle of CAB tablets to the subject on Day 1 to receive CAB dosing at home on Days 2 to 12 in Period 1
9. Dispense the bottle of CAB tablets to the subject on Day 15 to receive CAB dosing at home on Days 16 to 20 and Days 22 to 25 in Period 2; dosing on Day 21, 26, 27, and 28 is in the unit.
10. Dispense the bottle of RBT capsules to the subject on Day 15 to receive RBT dosing at home on Days 16 to 20 and Days 22 to 25 in Period 2; dosing on Day 21, 26, 27, and 28 is in the unit.
11. Plasma PK samples (2 mL of blood per sample) will be collected to measure CAB at the following time points: Period 1: predose (within 15 minutes prior to dose) on Day 13; and pre-dose (within 15 minutes prior to dose), 1, 2, 3, 4, 8, 12, and 24 hours after CAB dosing on Day 14. Period 2: pre-dose (within 15 minutes prior to dose) on Days 26 and 27 and pre-dose (within 15 minutes prior to dose) on Day 28 and, 1, 2, 3, 4, 8, 12, and 24 hours after CAB +RBT dosing on Day 28.
12. It is recommended that the Pharmacogenetic sample be collected on Day 1, but it may be collected at any time following administration of investigational product.

7.2. Screening and Critical Baseline Assessments

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

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. 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.

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

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

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

For this study, the Sponsor considers seizures as an AE of special interest (see Investigator's Brochure for further information). Where seizures or suspected 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 Appendix 4, Section 12.4).

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact. Refer to Section 7.3.1.3.
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.

- 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 4.

7.3.1.2. Method of Detecting AEs and SAEs

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?"

7.3.1.3. 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 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 4.

7.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) 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.

7.3.2. Pregnancy

- 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 5.

7.3.3. Physical Exams

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

An ocular assessment will be performed only for subjects who experience eye symptoms.

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

7.3.4. Vital Signs

- Vital signs will be measured in semi-supine position after 10 minutes rest and will include systolic and diastolic blood pressure and pulse rate. Temperature will also be obtained as part of the Vital Signs assessment.
- Measurements that deviate substantially from previous readings will be repeated immediately.
- Two (2) blood pressure (BP) and heart rate (HR) measurement will be taken at pre-dose on Day 1, at least 1 minute apart. The mean value recorded at pre-dose will be classified as baseline. Single BP and HR will be obtained at all other time points during the study. A single Temperature (TT) assessment will be obtained at Pre-dose as well as other time points during the study as specified in the Time and Event Table Section 7.1.

7.3.5. Electrocardiogram (ECG)

- Two (2) 12-lead ECGs measurements will be performed with the subject in a semi-supine position having rested in this position for at least 10 minutes beforehand.
- Measurements that deviate substantially from previous readings will be repeated immediately.

- Two (2) measurements will be taken at pre-dose on Day 1, at least 5 minutes apart. The mean value recorded at pre-dose will be classified as baseline. Single ECG measurements will be performed at all other time points. 12-lead ECGs will be obtained during the study using an ECG machine that automatically calculates the heart rate and measures mean PR interval, QRS, QT, and QTcF (QT corrected by Fridericia's formula) intervals.

7.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Section 7 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 labeled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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.

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 3.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
	WBC Count (absolute)		Eosinophils	
	Reticulocyte Count		Basophils	
	RDW			
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Total CO_2	GGT	Chloride	
	CPK			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• TB Quantiferon Gold • HIV antibody • Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb) • Hepatitis C antibody (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing			

Laboratory Assessments	Parameters
	potential only) • Alcohol and drug 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)
NOTES : 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.2 and Appendix 2.	

Abbreviations:
RBC- Red blood cells, WBC- White blood cells, MCV- Mean corpuscular volume, MCH- Mean corpuscular hemoglobin, RDW- Red cell distribution width, BUN- Blood urea nitrogen, SGOT- Serum glutamic-oxaloacetic transaminase, SGPT- Serum glutamic pyruvic transaminase, CO2 – Carbon dioxide, GGT- Gamma glutamyltransferase, CPK- Creatine phosphokinase

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 14 days 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. Pharmacokinetics

7.4.1. Blood Sample Collection

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

Collect whole blood (2 mL) sample into a properly labeled K3EDTA evacuated blood collection tube. Record the exact date and time of sampling in the CRF, as appropriate.

Immediately after collection, gently invert (DO NOT SHAKE) the evacuated blood collection tube 8-10 times to mix the K3EDTA 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.

Shipping procedures are provided in the Study Reference Manual (SRM).

7.4.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-BIB/TPR, GlaxoSmithKline. The details of the analysis will be included in the Study Reference Manual (SRM). Concentrations of CAB will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for parent compounds, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate Platform Technologies and Science (PTS), GlaxoSmithKline protocol.

7.5. Genetics

Information regarding pharmacogenetic (PGx) research is included in Appendix 4. 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.
- 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.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is designed to estimate the drug-interaction effect of RBT on CAB PK parameters. No formal hypothesis will be tested. An estimation approach will be used to evaluate the effect of RBT on CAB PK. Point estimates and corresponding 90%

confidence intervals (CIs) will be constructed for the comparisons of interest (test:reference).

9.1.1. Primary Comparisons of Interests

The primary comparisons will be made for the repeated dose PK parameters of CAB when given alone in Period 1 (reference treatment) and when co-administered with steady-state RBT in Period 2 (test treatment).

Primary Treatment Comparisons		
PK Parameters	**Reference Treatment**	**Test Treatment**
Plasma CAB Cmax, AUC(0- τ)	CAB 30 mg once daily X 14 days	RBT 300 mg once daily X 14 days + CAB 30 mg once daily X 14 days

The point estimates of the geometric least squares (GLS) mean ratio and the associated 90% CIs will be provided for the treatment comparisons (test:reference).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size of 15 to obtain 12 evaluable subjects was chosen based on an expected withdrawal rate of approximately 20% and the within-subject variability of CAB, to address the objectives of the study.

The within-subject variations in PK parameters from previous tablet administration in CAB studies [GlaxoSmithKline Document Number RM2008/00856/00, ITZ111839 and GlaxoSmithKline Document Number 2011N122099_01, LAI116181] were in the range of 6.7-7.8%, and 6.9-11.4%, for the CAB PK parameters AUC(0-τ)/AUC(0-∞) and Cmax respectively.

Based on a within-subject coefficient of variation (CVw) of 11.4% and a sample size of 12 evaluable subjects, it is estimated that the half width of the 90% confidence interval for the treatment difference on log-scale will be within 8.3% of the point estimate for AUC(0-τ) and Cmax. If the point estimate of the ratio of geometric means is 1, then 90% confidence interval will be approximately (0.92, 1.09)

9.2.2. Sample Size Sensitivity

Using sensitivity analysis assuming higher within-subject CVw of 22.8% and a sample size of 12 evaluable subjects, it is estimated that the lower and upper bounds of the 90% CI for the treatment difference on log-scale would be within 16.7% of the point estimate for AUC(0-t) and Cmax.

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment will be performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Safety Population

All subjects who enroll into the study and receive at least one dose of study drug will be included in the Safety Population. This will be the population for the safety analyses, and for summarization of baseline/demographic characteristics.

Pharmacokinetic Concentration Populations

The CAB PK Concentration Population will include all subjects who undergo plasma PK sampling and have at least one evaluable PK assay results. CAB assay results from samples collected from a subject with emesis occurring within 4 hours of the dose will not be considered as evaluable. These populations will be used for the concentration listing.

Pharmacokinetic Parameter Populations

The CAB PK Parameter Population for this study will include all subjects with CAB PK parameters estimated. These populations will be used for PK parameter listing. PK parameter populations will also be used for plotting of the individual concentration-time data.

Pharmacokinetic Summary Population

The CAB PK Summary Population for this study will include subjects who have CAB PK parameter estimates from both serial PK sampling time periods 1 and 2. These populations will be used for the concentration and PK parameters summary figures and tables and for the statistical analysis of PK parameter data.

9.3.2. Interim Analysis

No interim analysis will be performed.

9.4. Key Elements of Analysis Plan

Final analysis will be performed after the completion of the study and final datasets authorization.

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

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

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

Version 9.3 or higher of the Statistical Analysis Software (SAS) system will be used to analyze the data as well as to generate tables, figures, and listings.

Complete details will be documented in the Reporting and Analysis Plan (RAP).

9.4.1. Primary Analyses

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Pharmacokinetic Analyses

Pharmacokinetic analyses will be the responsibility of Clinical Pharmacokinetics Modeling & Simulation Department, Quantitative Sciences, within GlaxoSmithKline. Plasma CAB concentration-time data will be analyzed by non-compartmental methods with WinNonlin Professional 5.2 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve at the end of the dosing interval (AUC(0-τ)) and Cτ (plasma concentration at the end of the dosing interval).

Statistical Analysis of Pharmacokinetic Data

All of the PK parameters will be log-transferred, except tmax.

Pre-dose concentrations collected between Days 13-14 and Day 26-28 will be used to assess for achievement of steady-state of CAB when CAB is given with RBT.

Analysis of variance (ANOVA), considering treatment as fixed effect, will be performed using SAS Mixed Linear Models procedure to evaluate the effect of RBT on CAB PK parameters: AUC(0-τ) and Cmax, The ratios of geometric least square (GLS) means and associated 90% CIs will be estimated for the PK parameters AUC(0-τ) and Cmax.

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.

The point estimates of the geometric least squares (GLS) mean ratio for the PK parameters Cτ, t1/2 and CL/F and the associated 90% CIs will be provided for treatment comparisons (test:reference). The PK parameters will be log-transformed prior to analysis and treatment comparisons will be expressed as ratios on the original scale as

primary PK parameter. Plasma tmax will only be summarized with the descriptive statistics.

9.4.3. Other Analyses

The relationship between CAB exposure and pharmacodynamic (PD) endpoints (e.g., safety parameters) may be explored, if needed.

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

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

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

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
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- 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 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, 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 GSK Standard Operating Procedures.
- GSK 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 GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK 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, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

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

10.7. 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.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

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

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

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AMD	Age-related macular degeneration
ANC	Absolute neutrophil count
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-τ)	Area under the concentration-time curve over one dosing interval
AUC(0-12)	Area under the concentration-time curve over 12 hours
β-HCG	Beta-Human Chorionic Gonadotropin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CAB	Cabotegravir
CABG	Coronary artery bypass grafting
CI	Confidence Interval
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CO2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
CPDS	Clinical Pharmacology Data Sciences
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
Cτ	Concentration at the end of the dosing interval
%CV	Coefficient of variation for the mean
%CVb	Between-subject CV
CV	Coefficient of variance
CVw	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DDS	Drug Development Sciences
DILI	Drug Induced Liver Injury
dL	Deciliter
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
ECG	Electrocardiogram
FDA	Food and Drug Administration

FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GLS	Geometric Least-Squares
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
HBCs	High-burden countries
HBcAb	Positive Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
Hep C	Hepatitis C
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HR	Heart rate
HSV	Herpes simplex virus
HSR	Hypersensitivity Reactions
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
λz	Terminal phase rate constant
L	Liter
LA	Long Acting
MAC	Mycobacterium avium intracellulare
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
mm	Millimeter
msec	Milliseconds
PCTA	Percutaneous transluminal coronary angioplasty
PD	Pharmacodynamic
PD	pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
PTS	Platform Technologies and Science
RDW	Red cell distribution width

QC	Quality control
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RBT	Rifabutin
RIF	Rifampin/ Rifampicin
RNA	Ribonucleic acid
RPV	Rilpivirine
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SPM	Study Procedures Manual
SUSAR	Suspected, Unexpected, Serious Adverse drug Reaction
t½	Terminal phase half-life
τ	Dosing interval
TB	Tuberculosis
TEN	Toxic epidermal necrolysis
tmax	Time of occurrence of Cmax
UDP	Uridine 5'-diphospho-glucuronosyltransferase
UGT	UDP glucuronosyltransferase
ULN	Upper limit of normal
UK	United Kingdom
US	United States
WBC	White blood cells
WGS	Whole genome screen
WPW	Wolf Parkinson White syndrome
744	GSK1265744

Trademark Information

Trademarks of ViiV Healthcare
NONE

Trademarks not owned by ViiV Healthcare
Chiron RIBA
Mycobutin
SAS
WinNonlin

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

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the food and drug administration [FDA] premarketing clinical liver safety guidance).

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

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN

If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• 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, stabilise, 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, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td colspan="2">• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake 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</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that 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

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12.3. Appendix 3 - 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.

12.3.1. References

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12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. 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 judgment 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).

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.

12.4.2. 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.

12.4.3. AEs of Special Interest:

Seizure
Three cases of seizures have occurred in the CAB program cumulatively through 01 October 2016. 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.

When seizures or suspected 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.

12.4.4. 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.

12.4.5. 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.

IMPORTANT – PLEASE NOTE THE FOLLOWING STATEMENT:
For this study the above criteria regarding mild, moderate and severe will be used in combination with the Modified Division of AIDS Table for Grading Severity of Adult Adverse Experiences, December 2004 (Appendix 6). In the InForm electronic data capture system intensity of adverse events will be recorded using the following categories:

1 = Mild or Grade 1

2 = Moderate or Grade 2
3 = Severe or Grade 3
4 = Grade 4
- X = Not applicable

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.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via paper CRF

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

12.5. Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is in line with their preferred and usual lifestyle (true abstinence). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP and withdrawal are not acceptable methods of contraception.

1. Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label and does not contain a medication.
2. 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, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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.

12.5.2. 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 5. 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

- Will be withdrawn from the study.
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.5.3. References

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12.6. Appendix 6: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse 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

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

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

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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) Specify type, if applicable	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* Specify type, if applicable	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) Specify type, if applicable	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) Specify type, if applicable	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Seizures New Onset Seizure ≥ 18 years of age	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
PREGNANCY, PUERPERIUM, AND PERINATAL				
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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) Specify disorder	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt Report only one	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted
RESPIRATORY				
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress Report only one	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)
SENSORY				
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)

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
< 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
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cytokine Release Syndrome[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
< 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

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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Calcium, High (mg/dL; *mmol/L*) ≥ 7 days of age	10.6 to < 11.5 *2.65* to < *2.88*	11.5 to < 12.5 *2.88* to < *3.13*	12.5 to < 13.5 *3.13* to < *3.38*	≥ 13.5 ≥ *3.38*
< 7 days of age	11.5 to < 12.4 *2.88* to < *3.10*	12.4 to < 12.9 *3.10* to < *3.23*	12.9 to < 13.5 *3.23* to < *3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 > *ULN to* < *1.5*	6.0 to < 6.4 *1.5 to* < *1.6*	6.4 to < 7.2 *1.6 to* < *1.8*	≥ 7.2 ≥ *1.8*
Calcium, Low (mg/dL; *mmol/L*) ≥ 7 days of age	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 < *1.53*
< 7 days of age	6.5 to < 7.5 *1.63* to < *1.88*	6.0 to < 6.5 *1.50* to < *1.63*	5.50 to < 6.0 *1.38* to < *1.50*	< 5.50 < *1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 < *LLN to 1.0*	3.6 to < 4.0 *0.9 to* < *1.0*	3.2 to < 3.6 *0.8 to* < *0.9*	< 3.2 < *0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 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*
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*

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

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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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 109 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*
Urinalysis				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA

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

a. 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.
b. As per Bazett's formula.
c. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
d. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
e. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.
f. 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.
g. Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
h. Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.
i. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
j. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
k. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
l. WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.
m. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
n. 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.
o. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m2).
p. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
q. Male and female sex are defined as sex at birth.
r. 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.

12.7. Appendix 7: Toxicity Management

ANEMIA

Grade 1 (mild) hemoglobin decrease:

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

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

If the additional tests are within the normal range, 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:

5. peripheral blood smear
6. indirect bilirubin (abnormal if increased >50% from baseline)
7. haptoglobin (abnormal if ≤ 25 mg/dL)
8. 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:

9. peripheral blood smear
10. indirect bilirubin
11. haptoglobin
12. 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:

13. Temperature > 38.5°C
14. Lymphadenopathy
15. Pharyngitis
16. 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 Section 7.3 and Section 7.4

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:

17. Temperature > 38.5°C
18. Lymphadenopathy
19. Pharyngitis
20. 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 Section 7.3 and Section 7.4.

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 Section 7.3 and Section 7.4.

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. The subject should be closely followed every day until resolution of the reaction. The subject should remain on the study to be followed for safety and PK as outlined in Section 7.3 and Section 7.4.

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:

21. Temperature > 38.5°C
22. Eosinophilia
23. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
24. 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 Section 7.3 and Section 7.4.

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:

25. Temperature > 38.5°C
26. Eosinophilia
27. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
28. 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 Section 7.3 and Section 7.4.

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

12.8. Appendix 8: Protocol Changes

12.8.1. Protocol Changes for Amendment 01

Summary of Changes and Rationale for Amendment No. 1

Section	Section Title	Change	Rationale
12.5.1.	Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)	Clarification to abstinence was added.	This clarification was made to clarify that true abstinence established prior to the start of this study is an acceptable method of contraception when this is in line with the subjects preferred and usual lifestyle.
12.5.1.	Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)	The double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository) was removed from the list of highly effective methods for avoiding pregnancy in FRP.	This method of contraception is not considered a highly effective method for avoiding pregnancy in females of reproductive potential (FRP) for this protocol.

Modified text incorporated into protocol amendment 01:

12.5.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is in line with their preferred and usual lifestyle **(true abstinence).** Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), **declaration of abstinence for the duration of exposure to IMP** and withdrawal are not acceptable methods of contraception.

1. Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label and does not contain a medication

2. 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, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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.

Original text:

12.5.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label and does not contain a medication

2. 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, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

3. Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository).

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.

12.8.2. Protocol Changes for Amendment 02 (29-JUN-2017) from Amendment 1 (13-Apr-2017)

Where the amendment applies

This protocol amendment is applicable to all sites.

Current and Previous Protocols:

Summary of Changes and Rationale for Amendment No. 2

Section	Section Title	Change	Rationale
4.2	Treatment Periods and Duration	The Fasting requirement for Day 1 and Day 15 was removed.	Subjects are required to fast on Day 14 and Day 28 only.
12.4.3	Definition of Cardiovascular Events	Appendix 12.4.3- Definition of Cardiovascular Events has been removed from the Protocol Amendment No. 02.	The collection of Cardiovascular Events is not applicable to the 205712 study.

List of Specific Changes

Text which has been deleted from the protocol is indicated in Appendix 12 by ~~strike through~~ format.

Modified text incorporated into this protocol amendment (Protocol Amendment No. 2):

Section 4.2: Treatment Periods and Duration

Rationale for change:

Subjects are required to fast on Day 14 and Day 28 only.

REVISED TEXT:

Paragraph 4 Sentence 1

On Day 1, following completion of the required pre-dose measurements, the investigator or authorized study unit personnel will administer a single oral dose of 30 mg CAB to each subject ~~under fasting conditions~~ in the unit.

Paragraph 6 Sentence 1

On Day 15 following the completion of the required Day 14 safety assessments and PK collection, subjects will proceed to Period 2, where site staff will administer a single dose of RBT 300 mg and a single dose of CAB 30 mg ~~after an overnight fast of at least 6 hours~~ in the unit. Subjects will be discharged and dispensed a bottle of RBT and a bottle of CAB to be taken at home on Days 16-20.

Section 12.4.3: Definition of Cardiovascular Events

Rationale for change:

The collection of Cardiovascular Events is not applicable to the 205712 study.

REVISED TEXT:

~~**12.4.3. Definition of Cardiovascular Events**~~

~~**Cardiovascular Events (CV) Definition:**~~

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

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