TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase 2a, Multicenter, Randomized, Adaptive, Open-label, Dose Ranging Study to Evaluate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Cobicistat-boosted GSK2838232 Monotherapy Over 10 Days in HIV-1 Infected Adults

Compound Number: GSK2838232

Development Phase: IIA

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N227852_00	**2016-NOV-09**	**Original**
2015N227852_01	**2017-APR-26**	**Amendment No. 1**
Amendment 1 includes minor updates to Inclusion-Exclusion (IE) criteria, including clarification on use of pre- or post-exposure prophylaxis, and removal of exclusionary requirements related to concomitant medications and tobacco and alcohol use during the study. Guidance around relevant habits is included in the Lifestyle section of the protocol and adjustments were made to reduce restrictions on these requirements. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirements. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Furthermore, the serial ECG collection (up to 6h post-dose) was removed on Day 5. Finally, the post-study care guidance was updated to include an option for subjects to receive reimbursement for marketed ART for a limited period after completion of study treatment and follow up. Minor clarifications, reformatting of tables, re-numbering of sections and correction of typographical errors were also made throughout this amendment.		
2015N227852_02	**2017-MAY-24**	**Amendment No. 2**
Amendment 2 includes expansion of the eligible subject population to allow treatment experienced HIV-1 infected patients, in addition to treatment naive patients. Patients with a treatment history of a prior maturation inhibitor will still be ineligible. Slight modifications were made to include flexible language for enrolment into Part B to allow prioritization of one dose cohort or to open randomization into Part B cohorts in a parallel fashion. Also the upper limit of the BMI inclusion criteria was increased from 31 to 35 kg/m^2.		
2015N227852_03	**2017-JUN-15**	**Amendment No. 3**
Amendment 3 includes modification to the protocol Inclusion Criteria (#6) to ensure exclusion of treatment-experienced patients with limited remaining treatment options.		

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Regulatory Agency Identifying Number(s): 116,094

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200911

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:	
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Investigator Signature	Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 200911

Rationale

GSK2838232 is a novel human immunodeficiency virus (HIV-1) maturation inhibitor that is being developed for the treatment of HIV-1 in combination with other antiretrovirals.

Three clinical studies of GSK2838232 (n=53 healthy subjects) have been completed thus far. One study (Study 204953) completed at the end of 2016 and analysis of the data is ongoing. Healthy subjects have received GSK2838232 or placebo in single or repeated dose designs, to a maximum single dose of 250 mg or repeated dose (for 11 days) of 200 mg QD, in combination with ritonavir (RTV).

Study HMI116787 (completed November 2013) was the First Time in Human study of GSK2838232 and assessed safety and tolerability of escalating doses (5 mg to 100 mg), food effect, and the impact of steady-state ritonavir on GSK2838232 pharmacokinetics (PK). Following successful completion of 3-month toxicology studies in rat and dog in 2014, clinical studies 200912 and 200207 were initiated. These were double-blind, placebo-controlled, single (Study 200912) and repeat-dose (Study 200207) escalation studies to investigate the safety, tolerability, and PK of GSK2838232 alone and when co-administered with ritonavir 100 mg once daily (QD) for 8-11 days. Further assessment of an alternative formulation was also an objective in Study 200912.

Both studies were prematurely terminated/completed in March/April 2015 because of concerns over cardiovascular (CV) toxicity, in particular a clinical CV serious adverse event (SAE) whereby the Food and Drug Administrating (FDA) imposed a clinical hold. Following submission of long-term (6-month rat, 9-month dog) chronic toxicology data and follow up to the clinical SAE in November 2015, the hold was released in January 2016 and Study 204953 was initiated.

Study 204953 investigated the safety and PK of GSK2838232 in single and repeat-doses as well as the suitability of a new, capsule formulation. Doses of up to 250 mg GSK2838232/100 mg RTV (as single doses) or 200 mg GSK2838232/100 mg RTV (QD for 11 days) were studied. The final cohort of the study assessed unboosted GSK2838232 (200mg BID) for 11 days. The study completed at the end of 2016 and the data analys is ongoing.

These studies have shown GSK2838232 with or without RTV to be well tolerated and, together with daily RTV dosing (“boosting”), demonstrate a PK profile suitable for progression to HIV patients in this Phase IIa proof of concept 10-day, monotherapy study design. However, potential concerns over protease resistance necessitate a change to a pharmacoenhancer without antiviral effects in this study of GSK2838232 monotherapy. Therefore, for Study 200911, cobicistat (Tybost,150 mg QD) will be substituted for RTV.

The objective of Study 200911 is to understand the safety, PK and HIV antiviral profile of GSK2838232/cobicistat (GSK2838232/cobi) when given to HIV-infected, treatment naive, otherwise healthy adults. Approximately 10 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology, and PK data analysis,

approximately 8 subjects will be enrolled in each of between two and four Cohorts in Part B.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate antiviral activity of GSK2838232/cobi in HIV-1 infected patients during 10 days of monotherapy.	• Change from baseline (Day 1) in plasma HIV-1 RNA
• To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days.	• Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments.
• To characterize the pharmacokinetics of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days.	• GSK2838232 PK parameters following dose administration, as follows: **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Secondary	
• To explore the relationship between GSK2838232 exposure and change in plasma HIV-1 RNA	• GSK2838232 PK parameters Day 10 AUC(0-τ), Cmax, Cτ with Day 11 HIV-1 RNA change from baseline
• To assess the immunologic effect of GSK2838232/cobi when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ cell count to Day 11
• To explore the relationship between GSK2838232 exposure and safety or immunologic parameters, if appropriate.	• GSK2838232 PK parameters on Day 10: AUC(0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count

Objectives	Endpoints
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate
• To estimate GSK2838232 accumulation and to assess attainment of steady state following administration of GSK2838232/cobi for 10 days in HIV infected subjects.	• **Accumulation:** GSK2838232 PK accumulation ratios (R): Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively • **Steady State:** pre-morning dose concentrations (C0) on Days 2 through 11
• To examine dose proportionality of GSK2838232 pharmacokinetic parameters following GSK2838232/cobi dosing for 10 days in HIV infected subjects.	• Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax, and Cτ at different dose levels for the assessment of dose proportionality
Note: Other exploratory objectives and endpoints will be specified in the RAP	

Design, Treatment Arms and Duration

Approximately 34 HIV-1 infected subjects will be enrolled overall.

This study is a 10-day monotherapy, open-label, adaptive, dose ranging, repeat-dose study and will be conducted as two parts with an interim (go/no-go) analysis performed after Part A (Table 1). Part A, Cohort 1 will evaluate a safe and well-tolerated dose level of GSK2838232 that has been tested (with RTV) in prior Phase I studies and that targets a high inhibitory quotient (IQ) value. Following the completion of an interim analysis of those data and according to criteria defined later in the protocol, further cohorts of 8 subjects will then be studied in Part B in two or more cohorts (depending upon the data obtained in Part A).

The totality of this data will provide a full dose-response of GSK2838232 over a wide dose range to explore the safety and PK/pharmacodynamics (PD) relationship of GSK2838232 in HIV-1 infected subjects and facilitate choice of doses for Phase IIb studies.

Table 1 Study Design for 200911

	Part A: GSK2838232/cobi Once Daily x 10 days[1]		Part B: GSK2838232/cobi Once Daily x 10 days[1,2]		
Cohort	N	232 Dose (mg)	Cohort	N	232 Dose (mg)
1	10	100			
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B. All doses will be given with 150 mg cobicistat.
2. Part B GSK2838232 doses are an illustration of the projected doses per cohort. The actual doses for each cohort and number of cohorts are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobi co-dosing) may be added (the maximum dose in Part B would likely not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] was lower in HIV infected subjects than in healthy subjects at the same dose level).

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) was assessed and Study 205820, which plans to evaluate GSK2838232 at a dose of 500mg once daily (QD).

Subjects in both parts will have a screening visit within 30 days prior to first dose and a follow-up visit 7-14 days after the last dose. Maximum duration of study participation will be approximately 6 weeks.

HIV Drug Resistance: Following cessation of GSK2838232/cobi dosing for 10 days, there will be prolonged exposure to waning plasma concentrations of GSK2838232, because of the long t½ (i.e., in the "tail" of the PK profile). However, based on in vitro resistance passage data with GSK2838232 [and unlike with many other ARV therapies], there appears to be a limited likelihood of developing maturation resistance mutations in HIV-infected subjects due to its virologic profile.

Analysis

The primary objectives of this study are to investigate the safety, tolerability, PK and antiviral activity of 10 days repeated doses of GSK2838232/cobi in HIV-1 infected otherwise healthy subjects. Descriptive summaries will be provided for safety, PK, and HIV viral load data.

2. INTRODUCTION

GSK2838232 is a novel human immunodeficiency virus (HIV)-1 maturation inhibitor (MI) that is being developed for the treatment of HIV-1 infection in combination with other antiretrovirals (ART).

2.1. Study Rationale

This 'proof of concept (PoC)' open-label study is being conducted to characterize the acute antiviral activity, pharmacokinetics (PK), the relationship between PK and antiviral activity, and safety of GSK2838232 given with 150 mg once daily (QD) cobicistat (GSK283232/cobi), administered across a range of doses over 10 days in HIV-1 infected patients. A two-part adaptive and dose ranging design is to be applied in this study. Data from this study will be utilized to select doses for further studies in Phase IIb.

2.2. Brief Background

Combination antiviral therapy with inhibitors of HIV protease, integrase, entry and reverse transcriptase (RT) has demonstrated significant improvement in acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality over the last 10-15 years. Emerging multi-class drug resistant viral strains and long-term toxicities warrant development of new classes of antiretroviral therapies targeting various parts of the HIV-1 viral life cycle [Wainburg, 2010]. The inhibition of maturation of HIV-1 is a novel target for drug development, distinct from viral protease RT or integrase [Saxena, 2012; Qian, 2009]. HIV maturation is the final cleavage step of the capsidSp1 (transcription factor) polyprotein that generates the functional capsid p24 protein. This mechanism of action results in accumulation of the uncleaved p25 protein with subsequent improper assembly of the HIV core, resulting in a non-infectious virion. Gel-based mechanism of action studies suggest that compound GSK2838232 acts as a maturation inhibitor. Western Blot analysis shows inhibition of capsid-Sp1 cleavage and accumulation of p25 in the presence of GSK2838232.

Prior validation of this target was demonstrated with the HIV maturation inhibitor known as bevirimat (BVM; [Martin, 2007a; Martin, 2007b; Martin, 2008; NORVIR, 2013]). BVM reached Phase II studies in HIV patients; however, only modest reductions in plasma HIV-1 ribonucleic acid (RNA) concentrations were observed in Phase IIa monotherapy studies [Mahmood, 2006; Martin, 2007] and a pattern of polymorphic (differential) antiviral activity [Wainburg, 2010] led to termination of BVM development. The average decrease from baseline to Day 14 plasma HIV-1 ribonucleic acid (RNA) was 0.54 and 0.70 log10 copies/mL for 200 mg and 300 mg twice daily regimens (Table 2); all subjects achieved plasma BVM concentrations above the in vitro EC90. Responders, classified based on 5 polymorphisms in HIV-1 gag (at positions 369, 370, and 371), achieved an average 1.15 log10 copies/mL reduction in plasma HIV-1 RNA, while an average 0.17 log10 copies/mL reduction was achieved for non-responders.

Table 2 Summary of Bevirimat Antiviral Response and PK in a 14-day Monotherapy Study in HIV-infected Adults

BVM dosage regimen	Mean (SD) viral load change from baseline to Day 14	[2]IQ	Plasma BVM [1]Cmin (μg/mL)	Plasma BVM [1]Cmax (μg/mL)	Plasma BVM [1]AUC(0-τ) (μg.h/mL)
200 mg BID (N=14)	-0.54 (0.64)	1.70	46 (41, 51)	58 (53, 64)	632 (571, 699)
300 mg BID (N=18)	-0.70 (0.77)	2.67	72 (65, 80)	91 (84, 99)	973 (890, 1064)

1. Cmin, Cmax, and AUC reported as geometric mean (95% CI).
2. IQ=geometric mean Cmin/in vitro EC90; reported EC90=27 μg/mL; all subjects achieved IQ ≥1.

AUC(0-τ) = Area under the concentration-time curve over the dosing interval; BVM = Bevirimat; CI = Confidence interval; Cmax = Maximum plasma concentration; Cmin = Minimum plasma concentration; EC90 = 50% protection against resistant mutant HIV infection; IQ = Inhibitory quotient; SD = Standard deviation.

Early clinical data for BMS955176, a second generation maturation inhibitor, have been recently presented [Nowicka-Sans, 2015]. In a 10-day monotherapy trial in HIV-infected patients, plasma HIV-1 RNA was reduced at doses of between 40 mg and 120 mg QD. All doses were well tolerated. The maximum change, seen between 10 and 12 days after starting dosing, was about 1.5 log10, which is substantially better than the effect demonstrated with BVM and may indicate the maximum expected clinical effect of inhibiting this viral target.

Although BMS955176 is currently in Phase II studies in HIV-infected patients, there are no maturation inhibitors approved for the treatment of HIV infection. The uncertainties of early drug development and continuing need for novel ART, especially for heavily treated/experienced HIV-infected persons, support continued compound development. GSK2838232's low nanomolar in vitro potency against multiple HIV-1 gag polymorphisms and broader spectrum across multiple HIV-1 subtypes indicates it has utility in this setting.

2.2.1. Preclinical Summary

Nonclinical pharmacology

Virology

GSK2838232, in vitro, is an inhibitor of HIV maturation by preventing the cleavage of the HIV gag structural subunit p25 to p24. GSK2838232 is a potent antiviral agent with a mean 50% maximal inhibitory concentration (50% maximal inhibitory concentration [IC50]) value of 1.6 nM (range: 0.8 to 4.3 nM) when tested in a panel of 26 HIV-1 isolates with various polymorphic gag genotypes in peripheral blood mononuclear cells (PBMCs), suggesting that GSK2838232 can inhibit a broad spectrum of HIV isolates. In another PBMC assay, GSK2838232 showed potent antiviral activity in 59 of 60 isolates with IC50 values ranging from 0.22 to 5.1 nM. GSK2838232 also inhibited HIV-1 strains containing the consensus Sp1 QVT region or the V370A polymorphism in MT4 cells (IC50 = 0.73 to 0.81 nM).

In an MT2 cell-based assay utilizing recombinant viruses harboring gag and protease from subjects before and after a protease inhibitor (PI) based regimen, GSK2838232 inhibited 12 of 15 viruses with a mean IC50 value of 1.7 nM (range = 0.4 to 3 nM). The remaining 3 viruses were not inhibited by GSK2838232 up to the top concentrations tested at 400 nM. There was no correlation of PI sensitivity and susceptibility to GSK2838232. GSK2838232 resistance mutations were selected for by serial passage of virus in a SupT1 cell-based assay with increasing concentrations of GSK2838232. In the lab strain NL4-3 and gag/protease recombinant viruses, the resistance mutation A364V arose and resistance confirmed by site-directed mutagenesis. This resistance mutation maintains susceptibility to other classes of anti-retrovirals including PIs and non-nucleoside RT inhibitors.

GSK2838232 was tested in vitro in combination with two marketed PIs, atazanavir and darunavir. Using a dose-wise additivity model, GSK2838232A showed additive anti-viral activity with both PIs.

Secondary Pharmacology

In a secondary pharmacology study, GSK2838232 was tested against a panel of receptors, ion channels and transporters and demonstrated no significant effect (IC50 of ≤1 μM). It is important to note that the selectivity for antiviral activity of GSK2828232 compared to all tested off-target activities was >100-fold, and the potential for organ toxicity was characterized in the nonclinical toxicology studies (see below).

In safety pharmacology studies in male rats, there were no hemodynamic changes or neurobehavioral effects following single oral doses up to 300 mg/kg. A single oral dose of GSK2838232 at 30 mg/kg or 300 mg/kg produced reversible increases in respiratory tidal volume (32% and 36%, respectively) and derived minute volume (17% and 26%, respectively) at 6 hours after dosing. These doses did not produce any effect on respiratory rate, airway resistance or body temperature. There were no respiratory effects in rats given 5 mg/kg (mean maximum plasma concentration [C_{max}] 0.12 μg/mL; AUC_{0-24} 1.0 μg.h/mL based on Day 1 of the 4-week repeat dose study). These findings were not considered to suggest a safety concern in humans.

GSK2838232 at the maximum feasible concentration, limited by solubility, of 4.09 μM (3.31 μg/mL) caused no inhibition of human ether-a-gogo related gene (hERG) tail current in Human Embryonic Kidney 293 cells stably transfected with hERG cDNA, indicating a low probability for interaction at the hERG channel.

In conscious telemetered male dogs (n=4), a single oral dose of GSK2838232 at 60 mg/kg (C_{max} 0.59 μg/mL; AUC_{0-24} 8.7 μg.h/mL based on Day 1 exposure data from the 4-week oral repeat dose toxicity study) was associated with one episode of non-sustained ventricular tachycardia in one dog lasting ~1.2 seconds. There were no effects on arterial pressures, heart rate, or electrocardiogram (ECG) interval durations. An investigative safety pharmacology cardiovascular study was conducted in telemetered dogs given 60 mg/kg/day for 4 weeks with serial monitoring by echocardiography, cardiac biomarkers, qualitative and quantitative electrocardiology, microscopy, and transmission electron microscopy (TEM) of the heart.

There were no changes in echocardiography endpoints, ECG intervals, ECG waveforms, arterial pressures, heart rates, serum cTpnI, N-terminal prohormone of brain natriuretic peptide (NTproBNP), or in heart tissue as assessed by TEM. With routine microscopy, one treated dog had a single focus of degeneration/necrosis of the tunica media (moderate) in an extramural artery and another treated dog had localised, mixed-cell inflammation (mild) along the epicardium of the coronary groove. Both changes have been reported in normal beagles and were considered of uncertain relationship to treatment in the absence of changes in any other structural or functional cardiovascular endpoints. The 28-day exposures were similar to the previous 4-week toxicity study in dogs: the C_{max} range at 60 mg/kg/day in this investigative safety pharmacology study was 0.542 to 2.00 µg/mL and range of AUC_{0-24} was 6.04 to 35.7 µg.h/mL. In subsequent repeat-dose studies in dogs treated for up to 9 months with up to 70 mg/kg/day, no changes were evident in cardiac biomarkers (including cTpnI and NTproBNP), functional (including ECG waveform) or structural (including microscopic evaluation) cardiovascular endpoints at slightly higher exposures than those achieved than in previous studies. The end of the 9-month study, gender averaged C_{max} at 70 mg/kg/day was 1.95 µg/mL and AUC_{0-24} was 38.8 µg.h/mL. These studies support an absence of GSK2838232-related functional or structural effects on the heart in preclinical testing. The No Observed Adverse Effect Level (NOAEL) was established at 20 mg/kg/day (on the basis of mild hepatic findings) with an associated area under the curve at 24 hours (AUC24) of 16.2 µg.hr/mL and Cmax 0.847 µg/mL.

Pharmacokinetics and product metabolism in animals

The PK of GSK2838232 were investigated in the mouse, rat, and dog. The oral bioavailability of GSK2838232 was low to moderate (~6% to 40%) depending on the species and formulation. Plasma and blood clearance were low and the volume of distribution at steady state was high relative to total body water. The half-life of GSK2838232 was short in the mouse and rat, but moderate in the dog. Systemic exposure of GSK2838232 generally increased in a less than dose-proportional manner. In rats, there were no differences in systemic exposure between single and repeat-dose administration, or between males and females. In a 7-day study in dogs, systemic exposures were generally similar between males and females and after single and repeat dosing; however, in a 4-week study, systemic exposures were higher in females than in males in the high-dose group (60 mg/kg/day) and higher after repeat dosing than after a single dose. The distribution of radioactivity in male pigmented rats following a single oral administration of [^{14}C] GSK2838232 at a target dose level of 20 mg/kg showed radioactivity was rapidly absorbed and widely distributed throughout the body with all tissues, except the brain and spinal cord. There were no tissues that retained detectable levels of radioactivity at 28 days post dose. In a bile duct canulated rat study, 30% of the administered dose was excreted in the bile as an acylglucuronide. In the same study, unchanged drug and metabolites were eliminated primarily in the bile and feces, while a mean of <1% of the dose was eliminated in urine.

In vitro, GSK2838232 is highly protein bound (>99.9%) and has low passive permeability. In vivo evidence suggests active uptake of GSK2838232 by transporters in the rat liver.

After single oral doses of 5, 100, or 300 mg/kg, the average liver to plasma ratio was 51, 17, and 10, respectively. After 7 days of dosing at 30, 100, or 300 mg/kg/day, liver to blood ratios ranged from 10 to 16.

In the 13-week repeat dose studies in dogs given 35 mg/kg BID (70 mg/kg/day), heart tissue collected at necropsy had GSK2838232 concentrations 2.5 to 5-times higher than the 24-hour post-dose plasma concentrations, similar to the previous 4-week CV investigative findings. In the 13-week repeat dose studies in rats given 300 mg/kg/day, heart tissue collected at necropsy had GSK2838232 concentrations approximately 3 times higher than the 24-hour post-dose plasma concentrations, similar to the previous 7-day findings. Overall GSK2838232 did not appear to be highly concentrated in heart tissue after repeat dosing and suggests that accumulation upon chronic dosing is unlikely.

Routes of metabolism identified in liver microsomal incubations and rat, dog, and human hepatocytes were N-dealkylation, oxidation, oxidative deamination, and glucuronidation, alone or in combination, with no human-specific metabolites detected. N-dealkylated products and glucuronidation were observed in rat plasma and the bile. In general, in vitro metabolite profiles of the nonclinical species and human were qualitatively similar, such that all metabolites of [^{14}C] GSK2838232 observed in human hepatocyte incubations were observed in rat and/or dog. Minor to trace levels of potential aldehydes metabolites formed as a result of N-dealkylation and oxidative deamination were observed in rat, dog and humans.

GSK2838232 did not show evidence for glutathione adduct formation in rat or human liver microsomes. Data from pooled human liver microsomes along with recombinant cytochrome P450 (CYP) enzymes suggest that in vitro the oxidative metabolism of GSK2838232 was primarily mediated by CYP3A4. Preliminary in vitro investigations showed GSK2838232 did not inhibit CYP1A2, 2C9, 2C19, 2D6, 3A4 and was not a metabolism-dependent inhibitor of CYP3A4. No drug interaction risk was identified for co-administrated substrates of UGT1A1, 1A3, 1A6, 1A9, 2B7, and 2B15, OAT1, OAT3, OATP1B1, OATP1B3 or OCT2 at a clinical dose of 200 mg GSK2838232/ritonavir (predicted Cmax 0.32 μM). Extrapolation of the clinical risk (using FDA and EMA regulatory guidance) did indicate a risk for GSK2838232-mediated inhibition of UGT1A4 and of gut contributions of CYP3A4, P-gp, and BCRP at the same clinical exposure; however, the potential for clinically significant interactions via these mechanisms is predicted to be low (<2 fold change in AUC). GSK2838232 did show weak induction of CYP3A4 enzyme activity. However, based on the maximum predicted plasma concentrations and high protein binding, the potential for clinically significant drug interactions through CYP3A4 induction by GSK2838232 appears to be low.

The inclusion of cobicistat as a CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is unlikely to produce a significantly different profile of GSK2838232 ADME (and therefore systemic exposure); however, there have been no preclinical studies conducted with GSK2838232 and cobicistat to date.

Toxicology

GSK2838232 administered by oral gavage in repeat dose studies up to 6 months duration resulted in no adverse treatment-related effects in rats given up to 300 mg/kg/day QD.

In dogs given up to 70 mg/kg/day (35 mg/kg/day BID), adverse liver effects were noted at this dose in the 9-month repeat dose study. Though isolated, low grade changes in heart rate and cardiac troponin I (cTnI) had been noted in 4-week toxicity studies in rats and dogs; however, there were no treatment-related structural or functional cardiovascular changes in studies of 3 months and greater duration as assessed by echocardiography, ECG, microscopy, and cardiac biomarkers, indicating an absence of GSK2838232-related functional or structural effects on the heart in preclinical testing.

Only non-adverse treatment-related changes were noted in the definitive 6-month rat study, which included occasional salivation in animals given 300mg/kg/day and minimal clinical pathology changes without histologic correlates (transient clinical chemistry changes at ≥5 mg/kg/day and reversible urine chemistry changes at 300 mg/kg/day). The NOAEL in this study was considered to be 300 mg/kg/day (mean AUC[0-t] 21.3 μg.h/mL, mean Cmax 1.77 μg/mL [Week 26 values for males and females combined]).

As noted above, dogs given GSK2838232 at 70 mg/kg/day for 9 months had minimal to moderate pigmentation (consistent with bile) with minimal to mild mixed cell infiltration in the liver and isolated mild increases in alanine aminotransferase (ALT) activity. These findings were considered adverse, but were reversible after the 6-week off-dose period. The NOAEL for this dog study was considered to be the mid-dose level of 20 mg/kg/day (mean AUC[0-t] 16.2 μg.h/mL, mean Cmax 0.847 μg/mL [Week 39 values for males and females combined]).

Data from genotoxicity assessments suggest that GSK2838232 does not present a genotoxic hazard to humans.

During discussions with the FDA regarding the resolution of the clinical hold, the Agency recommended that the sporadic cardiovascular changes observed in the early (1-month) rat GLP study at the highest dose level (300 mg/kg/day) should be considered when defining the NOAEL and establishing a safe dose of GlaxoSmithKline (GSK) for the initiation of this study protocol. Accordingly, for the initial PK studies, the reference dose level of 30 mg/kg/day in the 1-month rat study was initially used to define the NOAEL and therefore the values for fold cover at maximum projected mean exposure and Cmax in human subjects were lower, at >2.5-fold. However, based on the cumulative clinical safety data through Cohort 5 of Study 204953, the designated NOAEL for the most sensitive species (i.e., 20 mg/kg/day in the 9-month dog study based on liver endpoints) is currently used for assessing fold-cover for projected clinical dosing in this study**.**

The inclusion of cobicistat as a CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is unlikely to produce a significantly different profile of GSK2838232 ADME (and therefore systemic exposure and toxicity); however, there have been no preclinical studies conducted with GSK2838232 and cobicistat to date.

Full details of non-clinical and clinical data may be found in the current Investigator's Brochure (IB) [GSK Document Number 2012N151889_03].

2.2.2. Clinical Summary of Safety and Pharmacokinetics

To date, GSK2838232 has been evaluated in three completed clinical studies with or without ritonavir (RTV) (GSK2838232/r). A fourth study (204953) completed late 2016 and data analysis is ongoing. Full details of the clinical results can be found in the Investigator's Brochure.

2.2.2.1. Clinical Summary of Safety

As of November 2016 fifty-three subjects had been exposed to GSK2838232 in 3 completed studies. One study (204953) completed in late 2016 and the analysis of results are ongoing (63 subjects were exposed to GSK2838232/r or placebo so far in this study). Overall, drug-related adverse events have been few and mild, and included headache, dizziness, fatigue, nausea, and palpitations and anxiety. Similarly, treatment-emergent laboratory abnormalities have also been few and mostly grade 1. There have been no discernible patterns, thus far, in terms of AEs or laboratory abnormalities.

One subject in study 200912 discontinued treatment with RTV due to an AE. A 47-year-old female who developed right upper quadrant abdominal pain, nausea and flatulence associated with grade 4 elevations in ALT and aspartate aminotransferase, and grade 2 elevations in total bilirubin (BIL). She was diagnosed with a common bile duct obstruction due to gallstones that spontaneously resolved. The Investigator assessed this AE as unrelated to study treatment.

Due to sporadic CV-related safety signals in the early animal studies (see Section 2.2.2), intense CV monitoring was in place for all four studies.

One AE occurred in HMI116787 that was initially considered a CV AE but after further evaluation was considered not to be of cardiac etiology. Two CV AEs occurred in 200207 that were initially considered possibly related to GSK2838232 exposure. However, further evaluation confirmed that there is a low likelihood that these events were due to GSK2838232 exposure. A summary of each event is provided in the IB.

In Study 204953, there have been a small number of CV-related events of any sort: There have been no serious adverse drug reactions, and no clinically significant drug-related abnormal findings for 12-lead ECGs, vital signs, safety laboratory results (including cardiac troponin I), or telemetry. The following cardiovascular AEs were observed during the course of the study but were not considered to be caused by GSK2838232 exposure:

- In Part 1A (Cohort 1), Period 2, a subject was withdrawn due to an AE (low hemoglobin) prior to GSK2838232 exposure Day -2. A replacement subject was brought in, but was not dosed with GSK2838232 or placebo because during the 2-day RTV run-in, on Day -1, the replacement subject met the stopping criteria for telemetry due to as brief occurrence of asymptomatic, NSVT prior to the first dose of GSK2838232 or placebo. Because the subject was excluded from the study prior to the first dose of investigational drug, the NSVT was not considered to be a serious and unexpected adverse drug reaction that would qualify for IND safety reporting.

- In Part 1A (Cohort 1), Period 3 (Period "3A" for the purpose of differentiating between 100 mg GSK2838232/r vs. 200 mg GSK2838232/r), one subject was discontinued prior to the first dose of study drug due to a series of cardiovascular findings (pre-ventricular contractions on telemetry). None of the findings were abnormal or atypical, but the investigator determined that this would not be a good etiology to have in a subject about to receive investigational drug. Because the event occurred prior to first dose of investigational drug, the finding was not considered to be due to GSK2838232 exposure.
- In Part 1A (Cohort 1), Period 3 (Period "3A" for the purpose of differentiating between 100 mg GSK2838232/r vs. 200 mg GSK2838232/r), one subject who had already been dosed on 2 previous occasions (with either GSK2838232 or placebo) was dosed for 2 days with RTV, and then on 05 May 2016 was dosed with either GSK2838232/r or placebo/r as scheduled. On the following day (06 May 2016), the subject experienced an asymptomatic, 6-beat run of NSVT, which was classified at the time as an SAE. Further monitoring, including continuous Holter monitoring revealed no further events. The subject had no troponin elevation throughout the study. After additional investigation it was determined that the NSVT had occurred after the subject had received placebo the previous day. Although the subject had received active on the two prior visits, the protocol allowed for sufficient washout between each dose. Therefore, because the subject had received placebo prior to experiencing the NSVT, the event was not considered to be due to GSK2838232 exposure or a serious and unexpected suspected adverse reaction that would qualify for IND safety reporting.
- In Part 2 (Cohort 6, 200mg/r), a 40 year old male enrolled in the study with no significant medical history experienced an asymptomatic ventricular triplet (NSVT) while asleep at 5:33am on Day 8 (of 11 days worth of dosing) approximately 21 hours after receiving 200 mg GSK2838232/r on the previous day at 8.25am. This event was noted by the site staff and the subject was assessed and found to have no associated clinical symptoms or complaints. The GSK medical monitor was notified. Because the subject was not symptomatic and this did not meet protocol-defined stopping criteria, the study was not unblinded at the time, and the subject was allowed to continue dosing. Dosing in the study is now complete and no further events have been noted. It was the assessment of the site PI and the GSK safety/monitoring team that a ventricular triplet can be seen in healthy volunteers on continuous Holter monitoring. Therefore neither the PI nor GSK considered this event to be a serious and unexpected suspected adverse reaction.

2.2.2.2. Study 204953 (completed); Pharmacokinetic Data

Study 204953 investigated the safety, tolerability, and PK of escalating doses of GSK2838232 as micronized API, with 100 mg RTV, initially as single doses and then as repeated doses for 11 days.

In addition, it evaluated the relative bioavailability of a single fasted dose of micronized API powder blend in capsules with RTV compared to powder-in-bottle for oral suspension with RTV and the effect of a normal fat meal on the bioavailability of a single dose of GSK2838232 in the capsule formulation with RTV. It will evaluate GSK2838232 exposure after repeated doses of unboosted GSK2838232 in the capsule formulation. Noncompartmental PK analysis was performed using scheduled sample times. The anaylsis of data from this study is ongoing; preliminary results are presented.

Pharmacokinetic analysis was performed on GSK2838232 plasma concentration-time data using nominal time following single doses of 50, 100, and 250 mg in combination with RTV in Part 1A of Study 204953 (Table 3). On average, GSK2838232 Cmax values were reached 4-6 hours after dosing. Terminal half-life values ranged from 15 to 28 hours across the three dose levels. Overall, broad dose proportionality was observed for Cmax and AUC(0-∞) values with ascending single doses of GSK2838232 (50, 100, and 250 mg with 100 mg RTV).

Table 3 Summary of Preliminary Pharmacokinetic Parameter Values after Single Doses of GSK2838232 in Combination with 100 mg Ritonavir (Study 204953, Part 1A)

Dose (mg)	n	t½ (h)	tlag (h)	tmax (h)	Cmax (ng/mL)	AUC(0-∞) (ng.h/mL)
50	8	22.7 (17%) (17.2-28.5)	0.188 (138%) (0-0.5)	3.63 (41%) (2.5-6.0)	17.2 (43%) (8.7-27.9)	458.6 (33%) (210.6-662.0)
100	6	18.0 (14%) (15.8-22.3)	0.167 (155%) (0-0.5)	6.00 (59%) (2.5-12.0)	25.2 (20%) (17.5-31.5)	890.5 (20%) (619.1-1053)
250	5	17.3 (6.4%) (15.5-18.6)	0 (-) (0-0)	5.50 (71%) (2.0-12.0)	60.7 (23%) (40.8-73.1)	1731 (29%) (1222-2505)

Data are presented as mean (CV) (minimum-maximum).

Study 204953 Part 1B was an open label, 2x2+1 three-period, crossover design, evaluating the relative bioavailability of the micronized API GSK2838232 powder blend in capsules compared to the PiB reference formulation for the first two periods, with the assessment of food effect on the capsule formulation in Period 3.

The relative bioavailability of the micronized powder blend in 50 mg hand-filled capsules compared to the micronized API as PiB for oral suspension was assessed as 100 mg GSK2838232 single doses with 100 mg RTV after two pre-doses (48 h) in the fasted state in a randomized crossover design in 12 subjects in the first two periods of Part 1B of Study 204953. Preliminary geometric mean AUC(0-∞) and Cmax values were approximately 45% and 60% higher, respectively, after administration in the capsule formulation compared to oral suspension from PiB (Table 4).

Table 4 Preliminary Assessment of Relative Bioavailability of Capsule Formulation vs. Powder-in-Bottle Formulation of GSK2838232 (Study 204953, Part 1B)

Parameter	Test	Reference	n	Ratio of Geometric Least Square Means	90% CI of Ratio
AUC(0-∞)	Capsule	PiB	12	1.43	(1.194,1.702)
Cmax	Capsule	PiB	12	1.58	(1.312,1.900)

PiB = powder-in-bottle.

The potential food effect with the capsule formulation was assessed as 100 mg GSK2838232 single doses with 100 mg RTV after two pre-doses (48 h) in the fasted state and with a normal fat meal in a non-randomized crossover design (fasted in either Period 1 or 2, fed in Period 3). Eleven subjects provided data for both dietary conditions. Preliminary geometric mean AUC(0-∞) and Cmax values were approximately 60% higher after administration in the capsule formulation with a normal fat meal compared to the fasted state (Table 5).

Table 5 Preliminary Assessment of the Effect of a Normal Fat Meal on GSK2838232 Exposure when Administered as a Capsule Formulation with Ritonavir (Study 204953, Part 1B)

Parameter	n	Capsule – food Geometric mean	Capsule – fasted Geometric mean	Ratio of geometric means (food/fasted)
AUC(0-∞) (ng.h/mL)	11	2414	1539	1.57
Cmax (ng/mL)	11	76.9	47.2	1.63

Repeat dose PK parameter values in Study 204953 Part 2 were determined on Day 1 and Day 11 using nominal time in Part 2 of Study 204953 (Table 6). After the Day 11 dose of GSK2838232 with RTV, exposure (Cmax, AUC[0-τ]) appeared to increase proportionally with the increase in dose level with the PiB and capsule formulations.

Table 6 Summary of Preliminary Pharmacokinetic Parameter Values on Day 1 and Day 11 during Repeated Dosing of GSK2838232 in Combination with 100 mg Ritonavir (Study 204953, Part 2)

Dose (mg)	n	t½ (h)	tlag (h)	tmax (h)	Cmax (ng/mL)	AUC(0-τ) (ng.h/mL)	Cτ (ng/mL)
Study Day 1							
20 (PiB)	6	-	0.417 (49%) (0-0.5)	3.67 (11%) (3.0-4.0)	12.2 (47%) (5.8-20.8)	189.4 (40%) (83.7-284.4)	6.1 (39%) (2.5-8.9)
50 (PiB)	6	-	0.167 (155%) (0-0.5)	3.00 (51%) (2.0-6.0)	18.7 (40%) (9.0-25.9)	288.7 (39%) (138.6-380.2)	9.5 (35%) (5.1-12.6)
100 (capsules)	6	-	0.167 (155%) (0-0.5)	2.25 (23%) (1.5-3.0)	48.4 (32%) (28.1-69.6)	664.1 (31%) (422.5-932.7)	21.6 (33%) (12.8-29.3)
200 (capsules)	6	-	0.083 (245%) (0-0.5)	2.50 (25%) (2.0-3.5)	79.4 (38%) (50.8-125)	1124 (39%) (636.7-1794)	38.9 (36%) (21.7-58.6)
Study Day 11							
20 (PiB)	6	19.2 (16%) (15.1-24.2)	-	5.00 (32%) (2.5-6.0)	27.4 (38%) (11.3-40.4)	474.3 (31%) (214.3-613.2)	15.3 (30%) (7.1-19.2)
50 (PiB)	6	27.3 (52%) (15.2-50.4)	-	3.50 (46%) (1.5-6.0)	58.0 (24%) (40.9-78.0)	1113 (23%) (762.6-1459)	38.8 (29%) (24.5-51.7)
100 (capsules)	6	17.9 (18%) (15.2-23.7)	-	4.00 (40%) (2.5-6.0)	133 (23%) (94.7-164)	2492 (27%) (1624-3301)	81.7 (30%) (45.9-113)
200 (capsules)	6	-[1]	-	3.33 (45%) (1.5-6.0)	240 (38%) (127-368)	4389 (45%) (2095-7161)	151 (46%) (67.8-250)

Data are presented as mean (CV) (minimum-maximum).

1. Concentration data were available up to 24 h after the Day 11 dose, and t½ values were not calculated.

2.2.2.3. Overall Summary/Conclusions of PK data

The original formulation used in the first three studies with GSK2838232 (HMI116787, 200207, and 200912) was SDD. Data from Study 200912 demonstrated that a change to the API formulation of GSK2838232 was feasible for future clinical studies. Study 204953 utilized micronized API powder in a bottle as well as in a capsule. The capsule was shown to be a viable solid dosage form for subsequent studies. A more detailed summary of the data from Study 204953 is in Section 2.2.2.2.

- GSK2838232 SDD did not overall demonstrate significant escalation in exposure from an increase in dose from 100 mg to 200 mg in a cross-study comparison. The API PiB formulation showed a proportional increase in AUC and Cmax for a 2-fold dose escalation from 100 mg to 200 mg.
- The observed tmax of the API form was significantly increased over the SDD formulation (the API formulation also increased tlag relative to SDD).
- The bioavailability of the GSK2838232 API formulation was on average 30-50% of the bioavailability of SDD formulation, but there was a large observed range of relative intra-subject exposures (11-150%).
- Both 10 mg SDD and 20 mg API showed a 10-fold or greater increase in AUC with steady-state RTV (100 mg QD for 10 days) with a smaller (≤4-fold) increase in observed Cmax. The t½ of GSK2838232 increased from 15-18 hours to 34-42 hours in the presence of steady-state RTV, regardless of formulation.
- After single doses of 50 to 250 mg GSK2838232 with RTV, increases in Cmax and AUC(0-∞) values were broadly proportional to the increase in dose. On Day 11 after repeated daily 20 to 200 mg doses of GSK2838232 with RTV, increases in Cmax and AUC(0-τ) values appeared to be proportional to the increase in dose with the PiB and capsule formulations.
- The relative bioavailability of the micronized API powder blend in capsules with RTV was approximately 45%-60% higher than the bioavailability of the micronized API administered as oral suspension from PiB with RTV.
- Co-administration of the micronized API powder blend in capsules with RTV and a normal fat meal resulted in an approximately 60% increase in geometric mean Cmax and AUC(0-∞) values compared to the fasted state with RTV (Study 204953).
- Variability remains fairly constant across formulations and boosted versus unboosted at around 30%-40% (moderate-high).
- Projections of potential future efficacious boosted GSK2838232 API regimens suggest that doses of 20 to 200 mg GSK2838232 API co-administered with RTV will result in mean trough values of at least 3-fold above the derived 90% maximal inhibitory concentration (IC90) target value (5 ng/mL). Even if protein binding has more impact than envisaged and causes a 5-fold increase in IC90 as seen in some preclinical virology studies, the predicted troughs will still be significantly higher than the 5-fold shifted IC90 (25 ng/mL) at doses of 50 mg or higher with RTV.
- The average and maximum AUC/Cmax values observed at the maximum dose studied to date are below NOAEL values in preclinical chronic toxicology studies (6-month rat, 9-month dog).

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To evaluate antiviral activity of GSK2838232/cobi in HIV-1 infected patients during 10-days of monotherapy.	• Maximum decline from baseline (Day 1) in plasma HIV-1 RNA
• To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days.	• Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments.
• To characterize pharmacokinetics (PK) of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days	• GSK2838232 PK parameters following dose administration, as follows: **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Secondary	
• To explore the relationship between GSK2838232 exposure and change in plasma HIV-1 RNA	• GSK2838232 PK parameters Day 10 AUC(0-τ), Cmax, Cτ with Day 11 HIV-1 RNA change from baseline
• To assess the immunologic effect of GSK2838232/cobi when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ cell count to Day 11
• To explore the relationship between GSK2838232 exposure and safety or immunologic parameters, if appropriate.	• GSK2838232 PK parameters on Day 10: AUC(0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate

Objectives	Endpoints
• To estimate GSK2838232 accumulation and to assess attainment of steady state following administration of GSK2838232/cobi for 10 days in HIV infected subjects.	• **Accumulation:** GSK2838232 PK accumulation ratios (R): Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively • **Steady State:** pre-morning dose concentrations (C0) on Day 2 through 11
• To examine dose proportionality of GSK2838232 PK parameters following GSK2838232/cobi dosing for 10 days in HIV infected subjects.	• Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax and Cτ at different doses levels for the assessment of dose proportionality
Note: Other exploratory objectives and endpoints will be specified in the RAP	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIa, multicenter, open-label, adaptive dose ranging, study to evaluate the antiviral effect, safety, tolerability, and PK of GSK2838232/cobi monotherapy over 10 days in HIV-1 infected adults who are not currently receiving ART therapy. Subjects who have received any prior maturation ihibitor therapy will not be eligible for this study. To minimize the number of subjects exposed to suboptimal doses, an adaptive and dose ranging design is applied in this study.

This study consists of a screening visit, a 10-day treatment period, and follow-up evaluations for 2 weeks following last dose.

Screening will be performed as the patients are identified, within 30 days of the first dose of study drug. Eligible HIV-1 infected subjects will receive study treatments for 10 days.

Table 7 Study Design for 200911

GSK2838232/cobi Once Daily for 10 days[1,2]					
Part A			**Part B**		
Cohort 1	**Dose (mg)**	**Interim Analysis**	**Cohort**	**N**	**(mg)**
N=10	100				
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B. All doses will be given with 150 mg cobicistat.
2. Part B doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobicistat co-dosing) may be added. (The maximum dose in Cohort B will likely not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] is lower in HIV-infected subjects than in healthy subjects at the same dose level).

After successfully completing screening evaluations, the first cohort will enroll 10 subjects to receive the 100 mg GSK2838232/cobi dose. Following interim analysis of Cohort 1, if warranted, Cohorts 2-4 will each enroll 8 subjects to receive a range of GSK2838232/cobi doses.

Day 1 – Day 10: Dosing

Subjects will report to the clinic for outpatient visits in the morning on Days 1 through 10 during the treatment period, except for the weekend (Days 6 and 7). Subjects will arrive each day prior to administration of the morning dose for safety and lab assessments, including HIV-1 RNA blood draws, as described in the Time and Events Table (Section 7.1). Subjects will begin receiving study drug in the morning of Day 1.

Serial, intensive blood PK samples will be collected on Day 1 (up to 24 hours post-morning dose) and Day 10 (up to 96 hours post-morning dose), and limited, single blood PK samples pre-morning doses on Days 3 through 9, except for the weekend. Subjects will be required to fast for 10 hours [overnight] prior to the morning check in on the intensive PK sampling days (Days 1 and 10). All dosing days will require co-administration of treatment with a light snack/meal per cobicistat labeling guidelines. All doses of study medication will be taken with 240 mL of water. Subjects will be required to stay in the clinic on Days 1 and 10 until all specified assessments are completed (8-12 hours post-dose). Following Day 10, subjects will be required to attend the clinic for follow up assessments including virological and PK blood sampling for up to 3 weeks.

Subjects will be given morning doses on Days 1 through 10 (except for the weekend) in the clinic. Weekend morning doses (Days 6 and 7) will be packaged and sent home for self-administration. After Day 11, the subjects will return frequently for assessments including blood draws for PK and HIV viral load. A diary card will be used to monitor dosing adherence.

Follow-up Visits:

Subjects will return to the clinic on Days 11, 12, 14 (±1 day), and 21 (±1 day) for PK and measurement of HIV-1 RNA levels, viral genotype/phenotype and safety assessments as shown in the Time and Events Table (Section 7.1).

4.2. Type and Number of Subjects

At least 34 subjects will be enrolled such that approximately 6-10 evaluable subjects complete a number of cohorts. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels as appropriate.

If subjects prematurely discontinue the study, additional subjects may be randomized and assigned to the same treatment cohort at the discretion of the Sponsor in consultation with the Investigator.

4.3. Design/Dose Justification

The fastest track to establishing antiviral potential of any novel HIV drug is to study a short course of monotherapy in HIV infected subjects. There is precedent for this across a number of classes of ART drugs.

Uncertainties over the impact of protein binding on the activity of GSK2838232 and the inherent potency of inhibiting the HIV maturation process as a target remain key objectives for the GSK2838232 program. This two-part adaptive design will allow an early understanding of the potential of GSK2838232 in combination with cobicistat (and by implication, RTV), while not exposing HIV-infected subjects to longer courses of what may be suboptimal doses and possible development of resistance.

Early clinical studies have indicated that in order to achieve reasonable IQ values likely to be associated with antiviral efficacy, GSK2838232 will need to be boosted with a pharmacoenhancer, such as RTV or cobicistat (in common with many CYP3A4 substrates).

There is no *a priori* intention to study GSK2838232 unboosted, unless: i) following the preliminary analysis of Part A Cohort 1, there is such pronounced antiviral activity that it would seem the estimates of projected IQ are low, in which case GSK2838232 may be evaluated in a subsequent cohort unboosted, or ii) the data from ongoing and planned healthy volunteer trials,Study 204953 (GSK2838232 200 mg BID unboosted) and Study 205820 (GSK2838232 500mg QD unboosted) support it.

4.3.1. GSK2838232 with Ritonavir

In Study HMI116787, a single dose of 10 mg GSK2838232 (SDD) given after 10 days of RTV 100 mg daily dosing (to steady state) demonstrated an increase in overall exposure (AUC) and Cmax by an average of 10.8- and 2.6-fold, respectively, compared to 10 mg GSK2838232 alone. Terminal phase half-life also increased from approximately 20 hours to 34 hours. This effect was presumably the result of an inhibition of a CYP3A4-mediated pathway. Studies 200912 and 200207 also indicated the utility of RTV in boosting GSK2838232 concentrations.

These data indicate the viability of studying a number of GSK2838232+RTV regimens in this PoC study. Predicted exposures following different GSK2838232 doses with steady-state RTV are presented in Table 8, based on the results of linear regression analyses of the preliminary Day 11 data in Study 204953 (dose levels of 20 to 200 mg) and assuming no significant differences in PK (ADME) between HIV-infected subjects and healthy subjects.

Table 8 Predicted Mean Steady-State GSK2838232 AUC(0-24), Cmax, and IQ, Following Repeated Dose Administration + RTV with Fold Cover to NOAEL

Dose (mg)	Projected AUC24 (ng.h/mL)[1]	Fold cover to NOAEL Dog[2]	Projected Cmax (ng/mL)[1]	Fold cover to NOAEL Dog[2]	IQ[3]
20+RTV	451	36	24	35	3.1
50+ RTV	1127	14	61	14	7.7
100+ RTV	2253	7.2	122	6.9	15
150+RTV	3380	4.8	183	4.6	23
200+RTV	4506	3.6	244	3.5	31

1. Predicted mean values based on linear regression analyses of preliminary Day 11 data in Study 204953.
2. Lowest NOAEL, 20 mg/kg/day obtained from 9-month study in dogs (AUC24 16200 ng.h/mL and Cmax 847 ng/mL)
3. Mean IQs derived from predicted Cτ/IC90 (with target of 5 ng/mL).

Cτ = Pre-dose (trough) concentration at the end of the dosing interval, IQ= inhibitory quotient.

The IQ following 20 mg to 200 mg GSK2838232/r QD is predicted to be >3 to >30-fold above the minimal target value (5 ng/mL) which was derived from preclinical virological assessment as 4 × EC50. No protein binding adjustment has been made because there was a minimal (≤5 fold) shift in assays where the effect of protein was assessed. If protein binding has more impact than anticipated, it is possible that the target Cmin value is approximately 25 ng/mL. In that scenario, projected IQ values at 200 mg/r QD would still be >5.

4.3.2. GSK2838232 with Cobicistat

There have been no preclinical or clinical studies with GSK2838232 and cobicistat to date; however, a review of the literature indicates that pharmacoenhancement of drugs that are known to have dominant CYP3A metabolic pathways is similar with either RTV or cobicistat [Kakuda, 2009; Elion, 2011; Gallant, 2013]. Thus, the use of cobicistat as the CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is expected to produce a similar profile of GSK2838232 ADME (and therefore systemic exposure). The pharmacokinetic data available after Part A Cohort 1 will confirm this assumption.

4.3.3. Interim Analysis

An evaluation of GSK2838232 safety, efficacy and PK data will be done after Part A Cohort 1, if the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects and the Bayesian probability from Cohort 1 is less than 70%, the study will not move forward into Part B, otherwise doses will be selected for evaluation in Part B. If pharmacokinetic exposure after the 100 mg GSK2838232/cobi dose is in the range of values observed after 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower (20 mg and/or 50 mg) and higher (200 mg) doses. The highest dose tested in Part B will be selected to result in exposures similar to those seen with 200 mg/r in Study 204953.

4.4. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2838232 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.4.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2838232		
Cardiovascular	Pre-clinical studies have shown the following findings: elevated heart rates, an isolated episode of non-sustained ventricular tachycardia and minimal to mild, sporadic troponin I elevations in dogs. A subsequent investigative cardiovascular study in telemetered dogs treated for 4 weeks did not replicate these effects. Isolated microscopic cardiovascular changes were noted (focal extramural arteritis and localized epicardial inflammation), however these changes were considered of uncertain relationship to GSK2838232 because similar findings occur at low incidence in normal beagles and there were no GSK2838232-related functional changes by telemetry and echocardiography, or changes in cTpnI and NTproBNP. In addition there was no correlation between histologic changes and plasma exposure or heart tissue concentrations of GSK2838232. 3, 6 and 9 month toxicology studies in rat and dog did not demonstrate any evidence of cardiovascular injury or impact on cardiovascular function. In the four GSK2838232 studies conducted so far there was no pattern of cardiovascular changes of clinical significance related to GSK2838232 and no clinically significant abnormality in electrocardiogram values other than the two SAEs documented and discussed. Review of published bevirimat preclinical and clinical safety data indicates no significant toxicities or AEs of interest, other than a 30% incidence of gastrointestinal symptoms (including diarrhea). There were no significant cardiovascular AEs reported in published clinical studies.	Subjects will be clinically monitored for any signs of myocardial injury (chest pain, shortness of breath, pain with inspiration), elevated heart rate or arrhythmias. Samples for the assessment of troponin will be taken. Baseline EKG and Holter (to use for screening and for later comparisons if needed) Exposures of GSK2838232 will be closely monitored in the clinical study so as to not exceed pharmacokinetic stopping criteria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cobicistat (Tybost)		
General	The cobicistat label includes the following information: TYBOST decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating TYBOST In one study investigating cobi+(atazanavir and tenofovir DF/emtricitabine) vs RTV+(atazanavir and tenofovir DF/emtricitabine), a higher frequency of reports of jaundice (6% and 3%) and ocular icterus (4% and 2%) were reported in the cobi group compared to the RTV group. Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides have been observed. The implications of these findings are unknown. The vast majority of available safety data has been obtained in combination studies with other ART. There are no warnings of obvious cobicistat-related adverse events or safety concerns.	Subjects will be closely monitored for any signs or symptoms potentially associated with cobicistat administration, in particularchanges in serum creatinine and liver chemistry.
HIV-1 Infection/Patient population		
HIV Resistance Propensity for co-meds and possible Drug-Drug Interactions (DDIs)	HIV Drug Resistance to unique mechanism Recognize HIV patients have a higher chance of comorbidities/diseases and a risk of taking a medicine or product contraindicated in the study	Closely monitor HIV viral load and genotypic resistance Strict adherence to protocol criteria around concurrent meds

4.4.2. Benefit Assessment

This study in HIV-1 infected but otherwise healthy subjects is a 10-day monotherapy design. It is anticipated that all subjects receiving GSK2838232 will experience anti-HIV effects whereby their (blood) HIV viral titres are reduced, until administration stops and the viral load returns to baseline levels. There is no expected longer term anti-HIV benefit to administration of GSK2838232. Participation in this study contributes to the process of developing GSK2838232 and other new therapies for the treatment of HIV infection.

4.4.3. Overall Benefit:Risk Conclusion

To date, 115 healthy subjects have received GSK2838232 in four completed studies.

Subjects have received single doses up to 200 mg SDD alone (studies HMI116787 and 200912), 250 mg API in combination with RTV (204953), and then in repeated daily doses of up to 50 mg SDD alone (200207) for 5 days or 200 mg in combination with RTV (204953) for 11 days.

There have been two cardiovascular SAEs reported from clinical studies where the subject was receiving GSK2838232 to date (one in 200207, one in 204953). Neither is thought likely to be due to GSK2838232.

There have been no other withdrawals due to drug-related AEs and no trends relative to laboratory toxicity. One subject was withdrawn in Part 1A of 204953 because of low haemoglobin lab values, thought unrelated to study drug or study procedures.

With respect to CV effects, with the exceptions noted, there have been no clinically significant changes in troponin, heart rate, blood pressure, ECG, or telemetry monitoring.

Subjects will also be at risk for AEs from cobicistat use and will be monitored closely for such events.

Given the preclinical profile and the clinical profile to date, the overall risk to HIV-1 infected but otherwise healthy subjects at the proposed GSK2838232 doses (with or without cobicistat) for 10 days is predicted to be low. Mean exposures at the highest dose studied are not projected to exceed NOAEL values obtained in chronic toxicology studies, further reducing potential risk.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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.

Approximately 10-12 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology and PK data analysis, approximately 8 subjects will be enrolled in each of Cohorts 2-4 in Part B. Eligible patients are those who are maturation inhibitor-naïve and who are not currently receiving ART therapy.

Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels or configurations (e.g., GSK2838232 alone).

If subjects prematurely discontinue the study, additional subjects may be enrolled .

5.1. Inclusion Criteria

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

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy (other than HIV infection) male or female as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. Defined as no other chronic medical conditions and taking no chronic medications.
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.
4. A creatinine clearance >80 mL/min as determined by Cockcroft-Gault equation [Cockcroft, 1976] CLcr (mL/min) = (140 – age) * Wt / (72 * Scr) (times 0.85 if female) where age is in years, weight (Wt) is in kg, and serum creatinine (Scr) is in units of mg/dL.
5. Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening.
6. Antiretroviral treatment naive or ART-experienced (maturation inhibitor naive). No current ART (last dose completed at least 6 weeks prior to the first dose of study drug). A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug. NOTE: Subjects with limited therapeutic options, including but not limited to those who have failed ≥2 antiretroviral regimens for any reasons or have documented resistance to >2 classes of antiretrovirals or have interrupted their treatment due to resistance, will not be eligible.

WEIGHT
7. Body weight ≥ 50 kg (110 lbs.) for men and ≥45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-35.0 kg/m^2 (inclusive)

SEX

8. Male or Female
 	
A female subject of reproductive or non-reproductive potential is eligible to participate if she is not pregnant (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test at screening and prior to first dose), not lactating, and at least one of the following conditions applies:
 	
Reproductive potential:
 	
Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. They will be counselled on safer sex practices
 	
There is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.
 	
Fertile females, who have an established, long-term lifestyle of sexual abstinence, or only same sex partners, require no other means of birth control.
 	
Non-reproductive potential:
 	
• Pre-menopausal females with one of the following:
  • Documented tubal ligation
  • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  • Hysterectomy
  • Documented Bilateral Oophorectomy
• Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
 	
Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until one week after the last dose of study medication.
 	
a. Vasectomy with documentation of azoospermia.
 	
b. Male condom plus partner use of one of the contraceptive options below:
  • Contraceptive subdermal implant that meets the SOP effectiveness criteria

including a <1% rate of failure per year, as stated in the product label

- Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
- Oral contraceptive, either combined or progestogen alone or Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

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.

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

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Alanine aminotransferase (ALT) and BIL >1.5xupper limit of normal (ULN; isolated BIL >1.5xULN is acceptable if BIL is fractionated and direct BIL <35%).
2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); HBV and/or HCV positive.
3. Subjects who have any other chronic medical condition, including CV, respiratory, neurologic, psychiatric, renal, gastrointestinal (GI), oncologic, rheumatologic, or dermatologic
4. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.

CONTRAINDICATIONS
5. 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.
RELEVANT HABITS
6. Chronic marijuana or use of other elicit medications (cocaine, heroin) is an exclusion criteria.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
7. Presence of hepatitis B surface antigen (HBsAg), positive (confirmed by Recombinant Immuno-Blot Assay [RIBA]) hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
8. Screening or baseline cardiac troponin I greater than the 99% cutoff (>0.045 ng/mL by the Dimension Vista CTNI assay).
9. A positive pre-study drug/alcohol screen.
10. Prior history of receiving an HIV maturation inhibitor
11. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.
12. 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).
13. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
14. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 30 days of study drug administration or anticipated need for such treatment within the study.
15. Treatment with immunomodulating agents (such as systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (such as hydroxyurea or foscarnet) within 30 days of study drug administration.
16. An active Center for Disease Control and Prevention (CDC) Category C disease except cutaneous Kaposi's sarcoma not requiring systemic therapy during the trial.
17. Treatment with any vaccine within 30 days prior to receiving study medication.
18. Exclusion Criteria for 24-Hour Screening Holter: • Any symptomatic arrhythmia (except isolated extra systoles). • Sustained cardiac arrhythmias (such as atrial fibrillation,flutter or supraventricular tachycardia (≥10 seconds) • Non-sustained or sustained ventricular tachycardia (defined as ≥3 consecutive

ventricular ectopic beats).

- Any conduction abnormality including but not specific to left or complete bundle branch block, atrioventricular [AV] block, high grade or complete heart block Wolff-Parkinson-White [WPW] syndrome etc.).
- Sinus Pauses >3 seconds.

19. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<45 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
*QTc interval	>450 msec	

*The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in 200911 will be Fridericia's formula.

- *Note: A heart rate from 100 to 110 beats per minute (bpm) can be rechecked by ECG or vitals within 30 minutes to verify eligibility.*
- Evidence of previous myocardial infarction (Does not include ST segment changes associated with repolarization).
- Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], WPW syndrome).
- Sinus Pauses >3 seconds.
- Any significant arrhythmia which, in the opinion of the principal investigator OR GSK medical monitor, will interfere with the safety for the individual subject.
- Non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats).

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 any SAEs.

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:

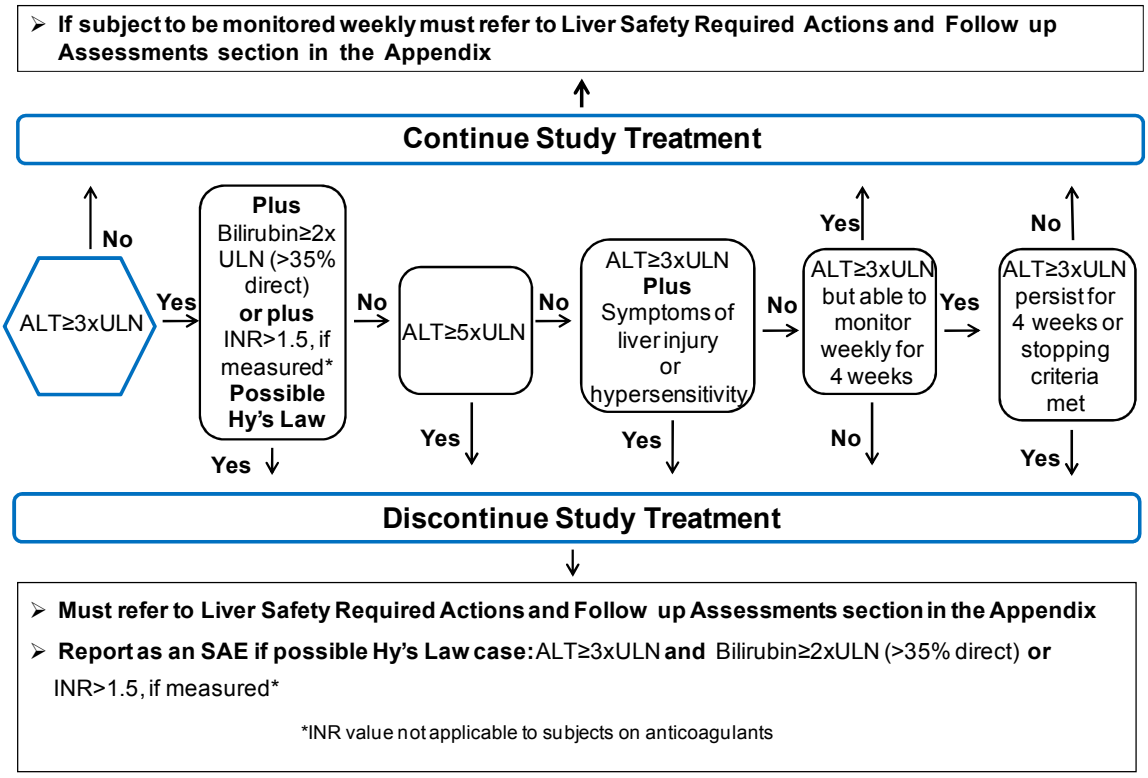
- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where 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 request has occurred in the site study records.

5.4.1. 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).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2, Section 12.2 and Section 12.3.

5.4.1.1. 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.

5.4.2. QTc Stopping Criteria

- The *same* 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.
  - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same 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 ECGs obtained over a brief (e.g., 5-10 minutes) recording period.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

5.5. Stopping criteria based on Adverse Events

Any grade 3 or higher treatment-related adverse events that occur in ≥2 subjects will be carefully reviewed and if considered clinically significant, dosing will be halted pending further discussion with the FDA. Any single treatment-related SAE will also trigger immediate evaluation and reporting processes in accordance with applicable regulations.

5.6. 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.

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Formulation description:	GSK2838232 powder blend in a capsule	Tablet
Dosage form:	Swedish orange, unmarked capsules (50 mg), and white, unmarked capsules (10 mg)	Orange, round, biconvex, film-coated tablets debossed with "GSI" on one side and plain faced on the other side providing 150 mg of cobicistat.
Unit dose strength(s)/ Dosage level(s):	50 mg capsule for 200 mg, 100 mg, 50 mg doses and 10 mg capsule for 20 mg doses	150 mg for 150 mg doses
Route/ Administration/ Duration:	Administered orally QD for 10 days	Administer orally, QD for 10 days

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Dosing instructions:	Administer with light meal and 240 mL of water.	Administer with light meal and 240 mL water.
Manufacturer/ source of procurement:	GSK	Gilead
Method for individualizing dosage:	Capsules supplied in high-density polyethylene bottles for individualized dosing by the clinic	Tablets supplied in bulk containers for individualized dosing by the clinic

6.2. Treatment Assignment

Subjects will be assigned to treatment (active) groups in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

6.3. Planned Dose Adjustments

Following the interim analysis of safety, virology and PK data from the first cohort of subjects in Part A, the option to adjust dose levels from those described exists. No dose will be administered that has an associated projected mean AUC or Cmax value higher than the most conservative NOAEL obtained from the chronic toxicity studies (i.e., from the 9-month dog toxicity study described in Section 2.2.1).

6.4. Blinding

This will be an open-label study. Treatment allocation and GSK2838232 dose levels in Part B will be determined after the analysis of Part A data.

Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for capsule/tablet storage and dispensing will be detailed in a Study Specific Technical Agreement/Memo or Pharmacy Manual, which will be accompanied by a Quality Agreement.

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.
- A Material Safety Data Sheet/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 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.

When subjects self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed through querying the subject during the site visits and documented in the source documents and case report form (CRF). A record of the number of study treatment(s) dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.7. Treatment of Study Treatment Overdose

For this study, any dose of GSK2838232 >200 mg+cobicistat within a 28-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose; however, in the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK2838232 can no longer be detected systemically (at least 10 days for GSK2838232)
- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

- 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 receiving GSK2838232 may opt to receive marketed antiretrovirals after the completion of 10 days of GSK2838232 dosing and study follow-up visits (through Day 21) eligible for sponsor company reimbursement up to a maximum of 90 days. The selection of antiretrovirals will be investigator-chosen.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing reimbursement for post-study treatment.

6.9. Lifestyle and/or Dietary Restrictions

6.9.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice from 7 days prior to the first dose of study medication until after the final dose.
- Doses will be given in the fed state (light breakfast), following overnight fasting (>10 hours).

6.9.2. Alcohol, Caffeine and Exercise

- During the study alcohol consumption should be limited to the following:
    - An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.
- Subjects should abstain from strenuous exercise during the treatment period.

6.10. Contraception

Female subjects can be of childbearing or non-child bearing potential.

Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. Although use of oral contraceptives is permitted, there is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.

Females of reproductive potential, who have an established, long-term lifestyle of sexual abstinence, or only same sex partners, require no other means of birth control.

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until one week after the last dose of study medication:

1. Vasectomy with documentation of azoospermia. 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.

OR

2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

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.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

- Acetaminophen at doses of ≤2 grams/day or NSAIDs are permitted for use any time during the study and their use documented in the CRF. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required.
- Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Subjects must notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications.

6.11.2. Prohibited Medications and Non-Drug Therapies

- Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 and at additional timepoints throughout the study. A positive result will lead to exclusion from the remainder of the study.

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 (Section 7.1), 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. In overview, subjects will be screened, begin dosing and then continue assessments through and for up to 2 weeks after the completion of dosing.

The following points must be noted:

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

    1. 12-lead ECG
    2. vital signs
    3. blood draws.

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

7.1. Time and Events Table

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Informed Consent	X																
Review inclusion/exclusion	X		X														
Demography including height, weight and BMI	X																
Brief physical			X														
Medical/medication/ drug/alcohol history	X		X														
CDC Classification	X		X													X	X
Prior antiretroviral therapy	X																
12-lead ECG[3]	X		X			X				X		X	X	X		X	X
Holter (24 hr)	X																
Vital signs[4]	X		X			X	X			X		X		X		X	X
Drug screen	X		X			X						X				X	
Hepatitis B Surface antigen and hepatitis C antibody testing	X																
Serum or urine β-hCG (WoCBP only)	X		X														X
Clinical lab tests (inc troponin)	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Fasting lipid panel	X																X
AE assessment[5]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Con Medication Review	X		X	X	X	X	X			X	X	X	X	X	X	X	X
HIV-1 RNA PCR[6]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Lymphocyte subsets[7]	X		X										X				
Plasma for genotype/phenotype[8]			X			X	X			X			X			X	X
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		X[14]
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Telephone call to IVRS[13]	X	X															X
Plasma for storage[15]			X	X	X	X	X			X	X	X	X	X	X	X	X
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

1. Screening will occur within 14 - 30 days prior to the first dose of study drug.
2. Table is set up for the weekend during dosing to occur on Days 6 and 7. If the weekend occurs on Days 5 and 6, perform all "Day 5" assessments on Day 7.
3. On Day 1, ECGs will be performed pre-dose , and then 1, 1.5, 2, 3, 4 and 6 hours post dose. The ECGs should be performed at least 5 minutes apart and preferably within 1 hour prior to dose. On Days 4 and 8, ECGs will be obtained prior to morning dosing and at 2, 4 and 6 hours post-dose. To accommodate scheduling, serial ECGs collected on Days 4 and 8 may be performed ± 1 day. On Day 10, ECGs will be performed pre-dose, and then 1, 1.5, 2, 3, 4 and 6 hours post dose. On Day 11, an ECG will be obtained prior to the 24-hour PK sample. ECGs will be performed in triplicate at all timepoints.
4. BP, RR, HR and temperature will be obtained at Screening (x1) and Day 1 pre-dose (x2). BP and HR will be obtained on Day 1 at 2 hours post-morning dose and on Days 4, 5 and 8 pre-dose. BP and HR will be obtained on Day 10 at pre-dose and 2 hours post-morning dose, and at day 12 and Follow-up (Day 21).
5. Only SAEs related to study participation will be collected between screening and Day 1. An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status.
6. On Days 1-5 and 8-10 samples for HIV-1 RNA PCR collected before morning dose. On Days 1, 10 and 11 two samples for HIV-1 RNA PCR will be collected 5-30 minutes apart. HIV-1 RNA PCR samples will also be collected on days 12, 14 & Follow-up (Day 21).
7. Lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+and CD8+counts).
8. Blood samples for phenotype and genotype will be collected at pre-dose on Days 1, 4, 5 and 8 in the morning on Day 11 and at follow-up.
9. Serial plasma samples (2 mL) for determination of GSK2838232 will be collected on Day 1 and Day 10 at pre dose (within 15 minutes prior to dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 (optional), and 24 hours (to occur on morning of Day 2 post-am dose and in the morning on Day 11) . Pre-dose PK samples (within 15 minutes prior to dose) will be taken on the mornings of Days 3, 4, 5, 8 and 9 and a single sample will be taken on Days 12 and 14.
10. Samples (2 x 0.5mL) of plasma for assessment of immunological markers at screen, baseline (pre-dose) and day 11
11. Subjects will receive a single dose of GSK2838232 and cobicistat each morning with a light breakfast meal and 240 mL of water from Day 1 to Day 10. Doses taken in the clinic will be administered after an overnight fast of at least 10 hours .On Days 6 and 7, doses will be self administered but confirmed by phone
12. PGx sample should be collected on Day 1.
13. A screening/registration call should be made to the IVRS to register the subject at screening. An additional call will be made to document a screen failure. A randomization call should be made to the IVRS system approximately one week prior to scheduled Day 1. Note: The randomization call must be made in order to have study drug on site for Day 1. Additional calls will be made every day that the subject has a scheduled study visit to the clinic. If a subject terminates the study prematurely a call should be made to the IVRS
14. Only if early termination visits occur during the treatment period.
15. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally these samples will be used when needed, such as when samples are lost or arrive at the laboratory unevaluable.

AE = Adverse event; CDC= Center for Disease Control and Prevention; ECG = Electrocardiogram; ET = Early termination; hCG = Human chorionic gonadotrophin; HIV = Human immunodeficiency virus; IVRS= Interactive Voice Response System; PCR = Polymerase chain reaction; PK=Pharmacokinetic.

7.2. Visit Windows

Screening (baseline to pre-dose): All screening assessments should take place within 14-21 days prior to the first dose. The screening visit window may be extended to 30 days upon discussion with the Medical Monitor (i.e.; subject has scheduling conflicts or any screening assessment needs to be repeated).

Days 4 and 8: Based on subject and clinic schedule, Day 4 and Day 8 serial (up to 6h post-dose) ECG assessments may be conducted ± 1 day.

Weekend(s): The T&E table is set up for study start (Day 1) to occur on a Monday and Days 6 and 7 to fall on the weekend. If the weekend occurs instead on Days 5 and 6, Day 5 assessments should be performed on Day 7. The study start (Day 1) may also be adjusted to allow visits with assessments to be conducted over the weekend based on subject and clinic schedule.

Assessments: The following applies to timing of procedures:

- Window for assessments ≤ 4 h post-dose = ± 5 minutes
- Window for assessments >4 and < 12 h post-dose = ± 15 minutes
- Window for assessments >12 h post-dose = ± 30 minutes

End of Treatment visit: should be within 14 days from last dose of study drug. If a subject is unable to return to the clinic for any reason site staff are encouraged to telephone the subject for assessment of adverse events.

7.3. 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.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.3.1. Holter Monitoring (Screening criteria)

The 24-hour Holter monitoring will be performed during the Screening period using a Holter monitoring device supplied by the Sponsor.

Analysis of the Holter tapes will consider the following:

- Heart rate (bradycardia and tachycardia)
- Normal and aberrant beats
- Number of supraventricular contractions, premature atrial contractions, premature ventricular contractions, couplets, triplets, and ventricular tachycardias
- Atrio-ventricular conduction defects
- Atrial fibrillation and flutter

7.4. Efficacy

7.4.1. HIV-1 RNA Sampling

Plasma for quantitative HIV-1 RNA will be collected at timepoints listed in the Time and Events Table in Section 7.1. To reduce sample variability, two plasma HIV-1 RNA samples will be collected on Days 1, 10, and 11.

An HIV-1 RNA PCR assay with a lower limit of detection (LLOD) of 50 copies/mL (ultrasensitive assay) will be used for post-baseline assessments. An HIV-1 RNA PCR assay with a LLOD of 400 copies/mL (standard assay) will be used for screening and baseline assessments and will include a re-test with and ultrasensitive assay for all baseline values below the LLOD. An HIV-1 RNA PCR assay with a LLOD of 2 copies/mL (supersensitive assay) may be used for exploratory analysis.

7.4.2. Lymphocyte Subsets by Flow Cytometry

Whole venous blood samples will be obtained from each subject for the analysis of lymphocyte subsets by flow cytometry at the timepoints listed in the Time and Events Table in Section 7.1.

Details concerning the handling, labeling and shipping of these samples will be supplied separately.

7.5. 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.

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

The definitions of an AE or SAE can be found in Appendix 5, Section 12.5.

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

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.5.1.3), at the timepoints specified in the Time and Events Table (Section 7.1). An AE enquiry will be made at each visit, where subjects will be specifically asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to Sponsor within 24 hours, as indicated in Appendix 5, Section 12.5.
- 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 5

7.5.1.2. 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?”
- “Have you experienced any alteration in personality, behaviour, mood or any altered mental status?”

7.5.1.3. 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, and non-serious AEs of special interest (as defined in Section 12.5) 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 5.

7.5.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 (Section 12.5.3) and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

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

The following disease-related events (DREs) are common in subjects with HIV-1 infection and can be serious/life threatening:

- events or outcomes listed in the CDC Classification System for HIV-1 Infections (see Appendix 9; Section 12.8)
- sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a serious adverse event).

These events will be recorded on the DRE page in the subject's CRF using the HIV Associated Conditions eCRF. These DREs will be monitored by the medical monitor and study team on routine basis.

However, if any of the following conditions apply, then the event should be reported as an SAE using the standard process:

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject,
  or
- The Investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.
  or

- Death occurring for any reason during a study, including death due to a disease related event, will always be reported promptly.

If either of the above conditions is met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly to GSK.

7.5.1.6. Regulatory Reporting Requirements for SAE

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs 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.

7.5.2. Pregnancy

- Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until one week post study
- If a pregnancy is reported then the investigator should inform GSK within 24hrs of learning of the pregnancy and should follow the procedures outlined in Appendix 7, Section 12.6.

7.5.3. Physical Exams

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

7.5.4. Vital Signs

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

7.5.5. Electrocardiogram (EGC)

- Triplicate 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.5.6. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments as defined in the Tables below must be conducted in accordance with the SRM and Protocol Time and Events Schedule (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled 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 SRM. 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 SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory:

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered in the CRF.

Haematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed below.

Table 9 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes with T-cell subsets	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Bicarbonates	Alkaline phosphatise	Albumin
	Troponin I			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]			

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 12.2 and Section 12.3
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 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.

7.6. Pharmacokinetics

7.6.1. Blood Sample Collection

Blood samples for analysis of GSK2838232 concentrations will be collected at the time points indicated in Time and Events Tables (Section 7.1).

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.6.2. Sample Analysis

Plasma analysis will be performed by Covance, Madison under the control of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS, GlaxoSmithKline. Concentrations of GSK2838232 will be determined in plasma using the currently approved bioanalytical methodology.

Once the plasma has been analyzed for GSK2838232 any remaining plasma may be analyzed qualitatively for other circulating metabolites and these results would be reported under a separate PTS protocol.

Raw data will be archived at the Covance, Madison facility.

7.7. Biomarker(s)/Pharmacodynamic Markers

7.7.1. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide plasma for viral genotype and phenotype analysis, at the times listed in the Time and Events Table in Section 7.1. Details concerning the handling, labeling and shipping of these samples will be supplied separately.

Genotypic and phenotypic analyses will be carried out by Monogram Biosciences using their GAG/PR and PR/RT formats, in which PCR amplification is used to generate HIV cDNA products including the Gag and the PR and RT coding regions, respectively. Phenotypic analyses of the GAG/PR region will include susceptibility to GSK2838232 . Analysis will be done on Day 1 and Day 11 samples. In the case of rebound HIV-1 viral load, analysis will be completed on samples corresponding to time point of rebound occurrence.

7.8. Genetics

Information regarding genetic research is included in Appendix 4, Section 12.4.

7.9. Value Evidence and Outcomes

Not required.

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 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

The primary objectives of this study are to investigate the safety, tolerability, and antiviral activity of GSK2838232 administered as monotherapy in combination with cobicistat in HIV-1 infected subjects, over a 10 day treatment period. The antiviral activity will be assessed by estimating plasma HIV-1 RNA max change from baseline during the study.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size for this study is based primarily on feasibility to provide adequate precision for the estimations.

Based on data from the short term monotherapy study of BMS-955176 PoC (AI468002) study and assuming viral load values for individual subjects follow a log-normal distribution, 1000 trial simulations in Fixed and Adaptive Clinical Trial Simulation (*FACTS*) software were conducted from the distribution with mean of change from baseline viral load drop on log scale at 1.0 to 1.5 copies and SD=0.4 and sample sizes=10 for Part A. Using Bayesian calculation with non-informative priors for the mean and weakly informative priors for the error parameters, Normal (0, 100) for mean and Inverse Gamma (0.35, 0.0875) for error parameters, the posterior probability to achieve a cutpoint 1.2 log was calculated for each simulated trial, and percentage of the trials with

posterior probability of viral load<-1.2log drop given true mean) ≥70% were calculated and are shown below in Table 10.

Table 10 Percentage of the trials with posterior probability>=70% for Part A

True Mean	Cutpoint	Posterior Prob>=70%
1.0	1.2	1.4%
1.1	1.2	9%
1.2	1.2	29%
1.3	1.2	59%
1.4	1.2	83%
1.5	1.2	96%

An Emax model with functional uniform priors [Bornkamp, 2014] was conducted using simulated data combining Part A and Part B with all doses. Success is defined as a posterior probability of the highest dose to achieve a cutpoint 1.2 log reduction in viral load. This was calculated for each simulated trial and the percentage of the trials with posterior probability greater or equal to 70% were also calculated and are shown below (Table 11). The table lists different viral load drop scenarios. The last scenario assumes the flat drop for all doses are 0.5. This scenario reflects the null hypothesis of no treatment effect. In this scenario 0% of the trials achieve the pre-specified decision rule for success.

Table 11 Percentage of the trials with posterior probability ≥70%

Cutpoint	Posterior Prob≥	Part A+ Part B mean VL drop for doses 200, 100, 50, 20	Part A+ Part B
1.2	70%	1.5, 1.4, 1.2, 0	99%
		1.5, 1.4, 1.2, 0.5	96%
		1.5, 1.4, 1.0, 0.5	93%
		1.5, 1.3, 1.2, 0.5	86%
		0.5, 0.5, 0.5, 0.5	0%

9.2.2. Sample Size Sensitivity

Similar simulations in FACTS were conducted from the distribution with mean of change from baseline viral load drop on log scale at 1.5 copies and SD=0.4 or 0.6 and sample sizes of 6-8 or 10 for Part A. Using Bayesian calculation, the posterior probability to achieve a cutpoint 1.2 log (in Table 12) was calculated for each simulated trial, and percentage of the trials with posterior probability greater than or equal to 70% was calculated and are shown below.

Table 12 Percentage of the trials with posterior probability ≥70% for Part A

True Mean	Cutpoint	Posterior Prob≥	Std for log10 VL	N=6	N=8	N=10
1.5	1.2	70%	0.4	90%	94%	96%
			0.6	75%	81%	84%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Intent to Treat Exposed Population (ITT)
The ITT-Exposed Population is defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received at least 1 dose of treatment and at least one post-baseline HIV-1 RNA measurement. This will be the primary population for the final efficacy analysis for all active treatment groups.

Per Protocol Population (PP)
The Per Protocol Population is defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received all doses and all post-baseline HIV-1 RNA measurement, with exceptions of major protocol deviation.

Safety Population
The Safety Population is defined as all subjects who are enrolled into the study with documented evidence of having received at least 1 dose of randomized treatment.

Pharmacokinetic Population
The PK Population will include all subjects who receive GSK2838232 and undergo plasma PK sampling during the study. Subjects for whom a plasma PK sample is obtained and assayed will be included in the listing of plasma GSK2838232 concentration-time data. Results from samples collected from a subject with emesis occurring within 4 hours of the dose will not be considered as evaluable.

9.3.2. Interim Analysis

An interim analysis of preliminary safety, tolerability, PK and antiviral activity will occur after subjects of Part A Cohort 1 complete their Day 13 visit. If the Cohort 1 dose is determined to be the highest dose based on this review (e.g., the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects), the Bayesian posterior probability that the log10 viral load decline from baseline is greater than a cut-point will be calculated. If the Bayesian probability from Cohort 1 is less than 70%, this will provide evidence to not move forward into Part B. Otherwise, the study team will review the data in order to make a dose selection decision for the subsequent Part B Cohorts. If the pharmacokinetic exposures after the 100 mg GSK2838232/cobi dose look similar to those obtained with 100 mg GSK2838232/r in

prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) GSK2838232 doses.

Maximum change and change from baseline in plasma HIV-1 RNA will be summarized by treatment or by assessment day. The proportion of subjects with plasma HIV-1 RNA <400 and <50 copies/mL will be summarized by treatment and assessment day. The analyses will be done for both PP and ITT exposed population if the two populations are not the same.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The 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 will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and %CVb for continuous variables, 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 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings. Complete details will be documented in the Reporting and Analysis Plan (RAP).

9.4.1.1. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library standards and data will be in CDISC format. No formal statistical analysis of the safety data will be conducted.

9.4.1.2. Efficacy Analyses

Both the PP and ITT Populations will be used for all efficacy analyses if there are dropouts. Plasma HIV-1 RNA max change and change from baseline during the study will be calculated for each subject on each assessment day.

Plasma HIV-1 RNA will be listed by treatment, subject, and assessment day and summarized by treatment and assessment day along with change from baseline.

Plots of mean and median plasma HIV-1 RNA actual and change from baseline data will be generated by treatment and assessment day.

- Plasma HIV-1 RNA change from baseline to the on-treatment nadir (maximum change) will be calculated for each subject and summarized by treatment.

Together, the data from Parts A and B will investigate the complete dose-response curve and the impact of lower doses on potential development of resistance. A dose-response curve will be fit to the data from Parts A & B using functional uniform priors.

9.4.1.3. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling and Simulation Department, GlaxoSmithKline. Plasma GSK2838232 concentration-time data will be analyzed by non-compartmental methods with WinNonlin Version 6.1 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:

Plasma GSK2838232 Pharmacokinetic Parameters to be Estimated:

Study Day	Parameters
1	AUC(0-24), Cmax, tmax, tlag, C24
10	AUC(0-τ), Cmax, tmax, t½, C0, Cτ, CL/F, R_AUC, R_Cmax, R_Cτ

Results based on samples collected from a subject with emesis within 4 hours of the dose will not be considered as evaluable.

All PK data will be stored in the R&D archives, GlaxoSmithKline.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline. Details of the statistical analyses will be provided in the RAP. An outline is provided below:

Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. Plasma GSK2838232 PK parameters, with the exception of tmax and tlag, will be log-transformed prior to analysis.

Dose proportionality of plasma GSK2838232 PK parameters from Day 1 [AUC(0-24) and Cmax] and Day 10 [AUC(0-τ) and Cmax] will be assessed using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI. The accumulation ratio (R) and steady-state assessments will be performed, if quality of the data permits. Comparisons of Day 10 with Day 1 PK for each dose will be used for the accumulation ratio (R) evaluation. Pre-dose concentrations between Days 7-10 will be used for steady-state assessment.

9.4.2. Secondary Analyses

9.4.2.1. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between various PK parameters (e.g., AUC, Cmax, Cτ, etc.) and PD measures (e.g., log10 reduction from baseline in plasma HIV-1 RNA on Day 11 or safety

parameters) will be explored using various models including Emax. The relationship between dose and PD measures will also be explored. Details of the PK/PD exploratory analyses will be provided in the RAP.

9.4.2.2. Viral Genotyping and Phenotyping Analyses

Viral genotypic/phenotypic data will be listed and descriptive summaries will be provided. Details of the analyses will be provided in the clinical virology report.

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 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 or designee 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 or designee 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.

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.

10.8. Review Committees

The Safety Review Team (SRT) is a GSK cross-functional team reviewing all available safety data related to the project, including in-stream data from this study, in an ongoing manner. The SRT is an internal GSK requirement put in place to ensure holistic evaluation of the safety profile of an investigational product with systematic, periodic and documented reviews of available safety data, with the appropriate communication and escalation of new findings that have the potential to impact patient safety

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

µg/mL	Microgram per millilitre
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredient
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUC(0-24)	Area under the concentration-time curve from zero (pre-dose) to 24 h
AUC(0-48)	Area under the concentration-time curve from zero (pre-dose) to 48 h
AUC(0-t)	Area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration
BCRP	Breast cancer resistance protein
BID	Twice daily
Bpm	beats per minute
BVM	Bevirimat
BIL	Bilirubin
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
C24	24 hour trough concentration
CDC	Center for Disease Control and Prevention
CI	Confidence interval
CL/F	Oral Clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CPK	Creatine Phosphokinase
CRF	Case report form
cTnI	Cardiac troponin I
CV	Coefficient of variation
CVb	Between-subject variability
CYP	Cytochrome P450
DDI	Drug Drug Interaction
DNA	Deoxyribonucleic acid
EC50	50% protection against resistant mutant HIV infection

ECG	Electrocardiogram
FC	Fold Changes
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FTIH	First time in Human Study
g	Gram
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour(s)
HBsAg	Hepatitis B surface antigen
hcG	Human chorionic gonadotrophin
HDPE	High density polyethylene
hERG	Human Ether-a-gogo Related Gene
HIV	Human Immunodeficiency Virus
IC50/90	50% or 90% maximal inhibitory concentration
IEC	International Ethics Committee
IQ	Inhibitory quotient
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous
IVRS	Interactive voice response system
kg	Kilogram
L	Litre
LLOD	Lower limit of detection
MC	Melanocortin
MedDRA	Medical Dictionary for Regulatory Activities
mg/mL	Milligram per millilitre
MI	Maturation inhibitor
mL	Milliliter
mRNA	messenger Ribonucleic Acid
ND	Not done
ng/mL	Nanogram per millilitre
nm	Nanometer
NO	Not observed
NOAEL	No Observed Adverse Effect Level
NTproBNP	N-terminal prohormone of brain natriuretic peptide
NSVT	Non-sustained ventricular tachycardia
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBL	Peripheral Blood Lymphocytes
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamics
PPD	Pharmaceutical Product Development
P-gp	P-glycoprotein
PHIV	Pseudo- HIV

PiB	Powder-in-bottle
PK	Pharmacokinetic
PoC	Proof of Concept
PI	Protease Inhibitor
QD	Once daily
RAP	Reporting and analysis plan
RIBA	Recombinant Immuno-Blot Assay
RT	Reverse Transcriptase
SAE	Serious adverse event
SDD	Spray Dried Dispersion
SRM	Study reference manual
t½	Terminal elimination half-life
TEM	Transmission Electron Microscopy
tlag	Time of first quantifiable concentration
tmax	Time of occurrence of Cmax
U	Units
UGT	Uridine 5'-diphospho-glucuronosyltransferase
Vz/F	Mean apparent oral volume of distribution
WPW	Wolff-Parkinson-White

Trademark Information

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Chiron RIBA
Inform
Monogram
Phoenix WinNonlin
SAS
Tybost (cobicistat)

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

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

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin1, 2</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR2</td><td colspan="2">ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic3</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted
• If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and may continue subject in the study</td><td colspan="2">• Viral hepatitis serology[4]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 24hrs after last dose[5]
• 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</td></tr>
</table>

for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high-performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week • 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. 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.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

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

12.4. Appendix 4: Genetic Research

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK2838232/RTV 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 or 2 ml saliva sample will be taken for Deoxyribonucleic acid (DNA) extraction. A 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/saliva 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/saliva 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/saliva 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.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT 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.

12.5.2. 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:
c. Results in death
d. 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.
e. 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.

f. 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

g. Is a congenital anomaly/birth defect

h. 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

i. 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.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Definition of Cardiovascular Events

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

12.5.4. 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. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by

the scale's developer.

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.5.5. 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.

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.
- By specific request, the investigator is obligated to report any grade 2 or higher "alteration in personality-behavior or in mood" or "altered mental status" adverse events that occur in subjects taking this drug, to GSK within 3 days.
- 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.

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data

on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.

- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF

- Facsim0ile 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.

SAE reporting to GSK via PIMS

- Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the Medical Monitor or protocol contact:
  - SAE listing
  - Demographic listing
  - Study treatment listing
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
- If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the Medical Monitor or protocol contact. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.6. Appendix 6: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24hrs 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 discontinue study medication and be withdrawn from the study
- This will only be included if either of the following apply:
- 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 report the event and submit it to GSK within 24hrs 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.

12.7. Appendix 7: Country Specific Requirements

No country-specific requirements exist.

12.8. Appendix 8: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events Version 1.0, December 2004; Clarification August 2009

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
DERMATOLOGIC				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE AND METABOLIC				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia **Report only one and specify location**	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< *30 years of age*	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] ≥ *30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< *30 years of age*	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
NEUROLOGIC				
Acute Central nervous system (CNS) Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay < *18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures *New Onset Seizure* ≥ *18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< *18 years of age* *(includes new or pre-existing febrile seizures)*	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
PREGNANCY, PUERPERIUM, AND PERINATAL				
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	World Health Organization (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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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 < Lower limit of normal (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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 Estimated glomerular filtration rate (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*
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Low Density Lipoprotein (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*
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY				
Absolute cluster of differentiation 4 (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

1. Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
2. As per Bazett's formula.
3. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
4. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.
6. Bone mineral density (BMD) t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.
7. Definition: A delivery of a live-born neonate occurring at ≥20 to <37 weeks gestational age.
8. Definition: A clinically recognized pregnancy occurring at <20 weeks gestational age.
9. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
11. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12. WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.
13. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
14. Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as Grade 2, if <10% of the total bilirubin.
15. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
16. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
17. Male and female sexes are defined as sex at birth.
18. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

12.9. Appendix 9: 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:

20. peripheral blood smear
21. indirect bilirubin (abnormal if increased >50% from baseline)
22. haptoglobin (abnormal if ≤ 25 mg/dL)
23. 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:

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. 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:

5. peripheral blood smear
6. indirect bilirubin
7. haptoglobin
8. 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 9.

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:

9. Temperature > 38.5°C
10. Lymphadenopathy
11. Pharyngitis
12. 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 10.5.

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:

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 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 10.5.

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 10.5.

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 24 hours via phone or fax. The subject should be closely followed everyday until resolution of the reaction. The subject should remain on the study to be followed for safety and PK as outlined in Section 10.5.

ALLERGIC REACTION

Grade 1 allergic reaction (Pruritis 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:

17. Temperature > 38.5°C
18. Eosinophilia
19. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
20. 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.

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:

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 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.

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

12.10. Appendix 10: Protocol Amendment Changes

12.10.1. AMENDMENT 1

Protocol Amendment 1 (26-Apr-2017) from the original protocol (09-Nov-2016)

Where the Amendment Applies

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

List of Specific Changes: (**bold** indicates text added and ~~strikethrough~~ indicates text removed)

Summary of Protocol Amendment Changes with Rationale

Amendment 1 includes minor updates to Inclusion criteria (IE) criteria, including clarification on use of pre- or post-exposure prophylaxis, and removal of exclusionary requirements related to concomitant medications and tobacco and alcohol use during the study. Guidance around relevant habits is included in the Lifestyle section of the protocol and adjustments were made to reduce restrictions on these requirements. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirements. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Furthermore, the serial ECG collection (up to 6h post-dose) was removed on Day 5. Finally, the post-study care guidance was updated to include an option for subjects to receive reimbursement for marketed ART for a limited period after completion of study treatment and follow up. Minor clarifications, reformatting of tables, re-numbering of sections and correction of typographical errors were also made throughout this amendment.

List of Authors

Rationale for change

The list of authors was updated based on internal GSK team personnel changes.

Revised Text

PPD

PTS, Ware, UK

GCSP, Stockley Park, UK

Infectious Diseases, Clinical, Upper Providence, PA, US

Clinical Statistics, GSK, Upper Providence, PA, US

HIV DPU, RTP, NC, US

Virology, HIV DPU, RTP, NC, US

PPD

CPMS, GSK, RTP, NC, US

HIV DPU, RTP, NC, US

Clinical Pharmacology, ViiV Healthcare, RTP, NC, US

PCPS, GSK, Upper Providence, PA, US

PCPS, GSK, Collegeville, PA, US

~~Clinical Statistics, PAREXEL, RTP, NC, US~~

~~Infectious Diseases, Clinical, Cambridge, MA, US~~

Medical Monitor/SAE Contact Information

Rationale for change

The sponsor and medical monitoring information was updated to reflect the current contact information for safety and medical monitoring.

Revised Text

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor/**SAE contact information**	PPD ~~MD~~ **Pharmaceutical Product Development (PPD) Safety Hotline**	PPD			~~Boston, MA~~**PPD, 929 North Front Street, Wilmington, NC 28401**
Secondary Medical Monitor	PPD MD				GlaxoSmithKline 1250 St Collegeville Rd Collegeville, PA 19426
~~SAE contact information~~	PPD ~~MD~~				~~Boston, MA~~

Synopsis: Design, Treatment Arms and Duration

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced. As synopsis being a standalone document, cross-referenced has been removed.

Revised Text

Fourth paragraph

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from ~~ongoing~~ Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) ~~is being~~ **was** assessed.

Sixth paragraph

HIV Drug Resistance: Following cessation of GSK2838232/cobi dosing for 10 days, there will be prolonged exposure to waning plasma concentrations of GSK2838232, because of the long t½ (i.e., in the "tail" of the PK profile). However, based on in vitro resistance passage data with GSK2838232 [and unlike with many other ARV therapies], there appears to be a limited likelihood of developing maturation resistance mutations in HIV-infected subjects due to its virologic ~~profile [GSK Document Number 2013N163221_00]~~.

Section 2 Introduction

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

GSK2838232 is a novel **human immunodeficiency virus (**HIV**)**-1 maturation inhibitor (MI) that is being developed for the treatment of HIV-1 infection in combination with other antiretrovirals (ART).

Section 2.1 Study Rationale

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

This 'proof of concept (PoC)' open-label study is being conducted to characterize the acute antiviral activity, pharmacokinetics (PK), the relationship between PK and antiviral activity, and safety of GSK2838232 given with 150 mg **once daily (**QD**)** cobicistat (GSK283232/cobi), administered across a range of doses over 10 days in HIV-1 infected patients. A two part adaptive and dose ranging design is to be applied in this study. Data from this study will be utilized to select doses for further studies in Phase IIb.

Section 2.2 Brief Background

Rationale for change

Abbreviation used on first instance has been defined.

Addition of abbreviation for AIDS in first paragraph

Combination antiviral therapy with inhibitors of HIV protease, integrase, entry and reverse transcriptase (RT) has demonstrated significant improvement in **acquired immunodeficiency syndrome** (AIDS)-related morbidity and mortality over the last 10-15 years.

Addition of abbreviation for RNA in second paragraph

Prior validation of this target was demonstrated with the HIV maturation inhibitor known as bevirimat (BVM; [Martin, 2007a; Martin, 2007b; Martin, 2008; NORVIR, 2013]). BVM reached Phase II studies in HIV patients; however, only modest reductions in plasma HIV-1 ribonucleic acid (RNA) concentrations were observed in Phase IIa monotherapy studies [Mahmood, 2006; Martin, 2007] and a pattern of polymorphic (differential) antiviral activity [Wainburg, 2010] led to termination of BVM development. The average decrease from baseline to Day 14 plasma HIV-1 **ribonucleic acid** (RNA) was 0.54 and 0.70 log10 copies/mL for 200 mg and 300 mg twice daily regimens (Table 2); all subjects achieved plasma BVM concentrations above the in vitro EC90. Responders, classified based on 5 polymorphisms in HIV-1 gag (at positions 369, 370, and 371), achieved an average 1.15 log10 copies/mL reduction in plasma HIV-1 RNA, while an average 0.17 log10 copies/mL reduction was achieved for non-responders.

Section 2.2.2 Clinical Summary of Safety and Pharmacokinetics

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Revised Text

To date, GSK2838232 has been evaluated in three completed clinical studies with or without **ritonavir** (RTV) (GSK2838232/r). A fourth study (204953) ~~is on-going as of 1st November~~ **completed late** 2016 **and data analysis is ongoing**. Full details of the clinical results can be found in the Investigator's Brochure.

Section 2.2.2.1 Clinical Summary of Safety

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Revised Text

~~Fifty~~ **As of November 2016 fifty**-three subjects ~~have~~ **had** been exposed to GSK2838232 in 3 completed studies. One study (204953) ~~is~~ **completed in late 2016 and the analysis of results are** ongoing (~~52 subjects have been~~ **63 subjects were** exposed to GSK2838232/r or placebo so far **in this study**). Overall, drug-related adverse events have been few and mild, and included headache, dizziness, fatigue, nausea, and palpitations and anxiety. Similarly, treatment-emergent laboratory abnormalities have also been few and mostly grade 1. There have been no discernible patterns, thus far, in terms of AEs or laboratory abnormalities.

Section 2.2.2.2 Study 204953 (completed); Pharmacokinetic Data

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Change in Heading

Section 2.2.2.2 Study 204953 (~~on-going~~ **completed**); Pharmacokinetic Data

Section 4.4.1 Risk Assessment

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
HIV-1 Infection/Patient population		
HIV Resistance Propensity for co-meds and possible **Drug-Drug Interactions (**DDIs**)**	HIV Drug Resistance to unique mechanism Recognize HIV patients have a higher chance of comorbidities/diseases and a risk of taking a medicine or product contraindicated in the study	Closely monitor HIV viral load and genotypic resistance Strict adherence to protocol criteria around concurrent meds

Section 5.1 Inclusion Criteria

Rationale for change

Changes were made to this inclusion criteria to clarify that prior use of pre- or post-exposure prophylaxis would not exclude a subject from participation as long as last dose was 6 weeks before starting study treatment.

Revised Text

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY

5 . Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening. No current and no prior ART. **(A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug).**

Section 5.2 Exclusion Criteria

Rationale for change

This exclusion criteria was removed and the guidance for use of concomitant medications was further addressed in Section 6.12, Concomitant Medications and Non-Drug Therapies. The Relevant Habits section of the Exclusionary criteria was also removed and addressed in Section 6.10, Lifestyle and/or Dietary Restrictions, with the exception of illicit drug use. Smoking and limited alcohol use are no longer exclusionary. Additional clarification added to note that positive Hepatitis C result would need to be confirmed by RIBA. Abbreviation used on first instance has been defined. Additional minor typographical errors were corrected.

Revised Text

~~CONCOMITANT MEDICATIONS~~
~~5. 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 GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.~~

RELEVANT HABITS
~~6. History of regular alcohol consumption within 6 months of the study defined as:~~ ~~• An average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.~~ ~~7. Smoking is an exclusion criteria for this study. Urinary cotinine levels indicative of~~

~~smoking at screening.~~ 6. Chronic marijuana or use of other elicit medications (cocaine, heroin) is an exclusion criteria.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

7 . Presence of hepatitis B surface antigen (HBsAg), positive **(confirmed by Recombinant Immuno-Blot Assay [RIBA])** hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.

19 . Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<45 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
*QTc interval	>450 msec	

*The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in ~~204953~~**200911** will be Fridericia's formula.

Section 6.1 Investigational Product and Other Study Treatment

Rationale for change

Minor typographical error corrected in this section.

Revised Text

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Method for individualizing dosage:	Capsules supplied in high-density polyethylene bottles for individualized dosing by the clinic	~~Capsules~~ **Tablets** supplied in bulk containers for individualized dosing by the clinic

Section 6.9 Treatment after the End of the Study

Rationale for change

Additional language was included in this section to allow subjects to opt to receive reimbursement from GSK for up to 3 months for marketed antiretroviral therapy (as

directed and prescribed by physician) based on the CDC guideline recommendations that patients be put on ARTs when diagnosed with HIV (test and treat guidelines).

Revised Text

~~Subjects will not receive any additional treatment from GSK.~~

Subjects receiving GSK2838232 may opt to receive marketed antiretrovirals after the completion of 10 days of GSK2838232 dosing and study follow-up visits (through Day 21) eligible for sponsor company reimbursement up to a maximum of 90 days. The selection of antiretrovirals will be investigator-chosen.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing ~~specific~~ **reimbursement for** post-study treatment.

Section 6.10.1 Meals and Dietary Restrictions

Previous section number 6.12

Rationale for change

This section was updated to remove language around meal provisions (language consistent for an in-patient trial). As this is an out-patient trial, it will be up to trial site to arrange when/how meals are provided during a subject's participation in the trial. The section 'Lifestyle and/or Dietary Restrictions' had no content described under it. The sections 'Meals and Dietary Restrictions' and 'Alcohol, Caffeine and Exercise' has been moved as sub-sections under the section 'Lifestyle and/or Dietary Restrictions', as the sub-sections are related to this section.

Revised Text

Second Bullet

Doses will be given in the fed state (light breakfast), following overnight fasting (>10 hours). ~~Lunch will provided ≥4 hours after the dose; water will be allowed ad libitum throughout.~~

Section 6.10.2 Alcohol, Caffeine and Exercise

Previous section number 6.13

Rationale for change

Adjustments were made to these lifestyle habits to eliminate restrictions on use of tobacco products, reduce restrictions on alcohol use and to allow occasional and light exercise during study treatment.

Revised Text

Alcohol, Caffeine~~, Tobacco~~ and Exercise

- ~~Subjects should refrain from alcohol for 48 hours before screening and then for 48 hours prior to admission and baseline assessments (on Day 1). Alcohol is then not permitted for the duration of the treatment period (through Day 10) and until the final follow-up visit.~~
- ~~Use of tobacco products is not allowed from screening until after the final follow-up visit~~
- ~~Subjects will~~ **During the study alcohol consumption should be limited to the following:**
  - **An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.**
- Subjects ~~will~~ **should** abstain from strenuous exercise ~~for 72 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities~~ during ~~studies (e.g., watch television, read).~~**the treatment period.**

Section 6.11 Contraception

Rationale for change

This section was updated to clarify that use of oral contraceptives are permitted during the study.

Revised Text

Second paragraph

Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. ~~**There**~~ **Although use of oral contraceptives is permitted,** t~~T~~here is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.

Section 6.12 Concomitant Medications and Non-Drug Therapies

Previous section number 6.14

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous section 6.12) and 'Alcohol, Caffeine and Exercise' (previous section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 6.10), the section has been re-numbered.

Deleted Text

- ~~Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 for each treatment period. A positive result will lead to exclusion from the remainder of the study.~~
- ~~The Principal Investigator must be informed as soon as possible about any medications taken from the time of screening until the subject is discharged from the study. Over-the-counter medications will not be permitted during the treatment period except as needed to treat an AE. If medication is needed, use should be restricted to 4 hours after dosing if possible.~~

Section 6.12.1 Permitted Medications and Non-Drug Therapies

Previous section number 6.14.1

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous Section 6.12) and 'Alcohol, Caffeine and Exercise' (previous Section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 10), the section has been re-numbered.

Revised Text

Addition of Second bullet

- **Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Subjects must notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications.**

Section 6.12.2 Prohibited Medications and Non-Drug Therapies

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous Section 6.12) and 'Alcohol, Caffeine and Exercise' (previous Section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 10), the section has been re-numbered.

Previous section number 6.14.2

Revised Text

- ~~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.~~
- **Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 and at additional timepoints throughout the study. A positive result will lead to exclusion from the remainder of the study.**

Section 7.1 Time and Events Table

Rationale for change

The Time and Events table was updated to remove the post-dose 12-lead ECG on Day 5, which remains in line with the FDA's guidance regarding days on which to perform post-dose (2 & 6 hours to capture near Tmax) ECGs. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Also minor clarifications were made and typographical errors were corrected.

Revised Text

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Informed Consent	X																
Review inclusion/exclusion	X		X														
Demography including height, weight and BMI	X																
Brief physical			X														
Medical/medication/ drug/alcohol history	X		X														
CDC Classification	X		X													X	X
Prior antiretroviral therapy	X																
12-lead ECG[3]	X		X			X	~~X~~			X		X	**X**	X		X	X
Holter (24 hr)	X																
Vital signs[4]	X		X			X	X			X		X		X		X	X
Drug screen	X		X			X						X				X	
Hepatitis B Surface antigen and hepatitis C antibody testing	X																
Serum or urine β-hCG (WoCBP only)	X		X														X
Clinical lab tests (inc troponin)	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Fasting lipid panel	X																X
AE assessment[5]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Con Medication Review	X		X	X	X	X	X			X	X	X	X	X	X	X	X
HIV-1 RNA PCR[6]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Lymphocyte subsets[7]	X		X										X				
Plasma for genotype/phenotype[8]			X			X	X			X			X			X	X
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		~~X~~**X**[14]
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														
~~**AE enquiry**~~[13]			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Telephone call to IVRS[13][14]	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Plasma for storage[15]			**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

1. Screening will occur within **14-**30 days prior to the first dose of study drug.
2. Table is set up for the weekend during dosing to occur on Days 6 and 7. If the weekend occurs on Days 5 and 6, perform all "Day 5" assessments on Day 7.
3. On Day 1, ECGs ~~(x2)~~ will be performed pre-dose , and then 1, 1.5, 2, 3, 4 and 6 hours post dose. The ~~pre-dose~~ ECGs should be performed at least 5 minutes apart and preferably within 1 hour prior to dose. On Days 4~~, 5~~ and 8, ECGs will be obtained prior to morning dosing and at 2, 4 and 6 hours post-dose. **To accommodate scheduling, serial ECGs collected on Days 4 and 8 may be performed ± 1 day.** On Day 10, ECGs ~~(x2)~~ will be performed pre-dose, and then 1, 1.5, 2, 3, 4 and 6 hours post dose. On Day 11, an ECG will be obtained prior to the 24-hour PK sample. **ECGs will be performed in triplicate at all timepoints.**
4. BP, RR, HR and temperature will be obtained at Screening (x1) and Day 1 pre-dose (x2). BP and HR will be obtained on Day 1 at 2 hours post-morning dose and on Days 4, 5 and 8 pre-dose. BP and HR will be obtained on Day 10 at pre-dose and 2 hours post-morning dose, and at **day 12 and** Follow-up **(Day 21)**.
5. Only SAEs related to study participation will be collected between screening and Day 1. **An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status.**
6. On Days 1-5 and 8-10 samples for HIV-1 RNA PCR collected before morning dose. On Days 1, 10 and 11 two samples for HIV-1 RNA PCR will be collected 5-30 minutes apart. **HIV-1 RNA PCR samples will also be collected on days 12, 14 & Follow-up (Day 21).**
7. Lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+and CD8+counts).
8. Blood samples for phenotype and genotype will be collected at pre-dose on Days 1, 4, 5 and 8 in the morning on Day 11 and at follow-up.
9. Serial plasma samples (2 mL) for determination of GSK2838232 will be collected on Day 1 and Day 10 at pre dose (within 15 minutes prior to dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 **(optional),** and 24 hours **(to occur on morning of Day 2** post-am dose and **in the morning on Day 11)** . Pre-dose PK samples (within 15 minutes prior to dose) will be taken on the mornings of Days 3, 4, 5, 8 and 9 and a single sample will be taken on Days 12 and 14.
10. Samples (2 x 0.5mL) of plasma for assessment of immunological markers at screen, baseline (pre-dose) and day 11
11. Subjects will receive a single dose of GSK2838232 and cobicistat each morning with a light breakfast meal and 240 mL of water from Day 1 to Day 10. Doses taken in the clinic will be administered after an overnight fast of at least 10 hours .On Days 6 and 7, doses will be self administered but confirmed by phone
12. PGx sample should be collected on Day 1.

~~13. An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status~~

13. A screening/registration call should be made to the IVRS to register the subject at screening. An additional call will be made to document a screen failure. A randomization call should be made to the IVRS system approximately one week prior to scheduled Day 1. Note: The randomization call must be made in order to have study drug on site for Day 1. Additional calls will be made every day that the subject has a scheduled study visit to the clinic. If a subject terminates the study prematurely a call should be made to the IVRS
14. Only if early termination visits occur during the treatment period.
15. **Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally these samples will be used when needed, such as when samples are lost or arrive at the laboratory unevaluable.**

AE = Adverse event; CDC= Center for Disease Control and Prevention; ECG = Electrocardiogram; ET = Early termination; hCG = Human chorionic gonadotrophin; HIV = Human immunodeficiency virus; IVRS= Interactive Voice Response System; PCR = Polymerase chain reaction; PK=Pharmacokinetic.

Section 7.2 Visit Windows

Rationale for Addition

Visit/procedure windows were included to allow more flexibility with scheduling of assessments.

New Section

Screening (baseline to pre-dose): All screening assessments should take place within 14-21 days prior to the first dose. The screening visit window may be extended to 30 days upon discussion with the Medical Monitor (i.e.; subject has scheduling conflicts or any screening assessment needs to be repeated).

Days 4 and 8: Based on subject and clinic schedule, Day 4 and Day 8 serial (up to 6h post-dose) ECG assessments may be conducted ± 1 day.

Weekend(s): The T&E table is set up for study start (Day 1) to occur on a Monday and Days 6 and 7 to fall on the weekend. If the weekend occurs instead on Days 5 and 6, Day 5 assessments should be performed on Day 7. The study start (Day 1) may also be adjusted to allow visits with assessments to be conducted over the weekend based on subject and clinic schedule.

Assessments: The following applies to timing of procedures:

- **Window for assessments ≤ 4 h post-dose = ± 5 minutes**
- **Window for assessments >4 and <u>< 12 h post-dose = ± 15 minutes</u>**
- **Window for assessments ><u>12 h post-dose = ± 30 minutes</u>**

End of Treatment visit: should be within 14 days from last dose of study drug. If a subject is unable to return to the clinic for any reason site staff are encouraged to telephone the subject for assessment of adverse events.

Section 7.3.1 Holter Monitoring (Screening criteria)

After addition of new section before this section, the section numbers from this section until Sections under 7.0 are re-numbered using the next available section number.

Rationale for Change

Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirement to allow flexibility based on clinic and subject schedule.

Revised Text

The 24-hour Holter monitoring ~~should only~~ **will** be performed ~~at~~ **during the** Screening ~~after the subject has met all other inclusion criteria.~~ **period using a Holter monitoring device supplied by the Sponsor.**

Analysis of the Holter tapes will consider the following:

- Heart rate (brady**cardia** and tachycardia)

- Normal and aberrant beats
- Number of supraventricular contractions, premature atrial contractions, premature ventricular contractions, couplets, triplets, and ventricular tachycardias
- Atrio-ventricular conduction defects
- Atrial fibrillation and flutter

Section 7.5.1.1 Time period and Frequency for collecting AE and SAE information

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

Bullet 4

- All SAEs will be recorded and reported to ~~GSK~~ **Sponsor** within 24 hours, as indicated in Appendix 5, Section 12.5.

Section 9.3.2 Interim Analysis

Rationale for Change

Minor corrections and clarifications were made to this section.

Revised Text

An interim analysis of preliminary safety, tolerability, PK and antiviral activity will occur after subjects of Part A Cohort 1 complete their Day 13 visit. If ~~based on this review~~ the Cohort 1 dose is determined to be the highest dose **based on this review** (e.g**.,** the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects), the Bayesian posterior probability that the log10 viral load decline from baseline is greater than a cut-point will be calculated. If the Bayesian probability from Cohort 1 is less than 70%**,** this will provide ~~evidenceto~~ **evidence to** not move forward into Part B. Otherwise, the study team will review the data in order to make a dose selection decision for the subsequent Part B Cohorts. If the pharmacokinetic exposures after the 100 mg GSK2838232/cobi dose look similar to those obtained with 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) **GSK2838232** doses.

Maximum change and change from baseline in plasma HIV-1 RNA will be summarized by treatment or by assessment day. The proportion of subjects with plasma HIV-1 RNA <400 and <50 copies/mL will be summarized by treatment and assessment day. The analyses will be done for both PP and ITT exposed population if **the** two populations are not the same.

Section 10.3 Quality Control (Study Monitoring)

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

First Bullet

In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors **or designee** 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.

Section 10.5 Study and Site Closure

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

First Bullet

Upon completion or premature discontinuation of the study, the GSK monitor **or designee** 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.

Section 11 References

Rationale for Change

Have mentioned the references as per GSK style guide and template.

Revised Text

Elion R, Cohen C, Gathe J, Shalit P, Hawkins T, Liu HC, **et al**. ~~Mathias AA, Chuck SL, Kearney BP, Warren DR.~~ Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine.tenofovir df in the initial treatment of HIV infection. *AIDS*. 2011; 25:1881-1886.

Gallant JE, Koenig E, Andrade-Villaneuva J, Chetchotisakd P, deJesus E, Antunes F, Arastéh K, **et al**. ~~Moyle G, Rizzardini G, Fehr J, Liu Y, Zhong L, Callebaut C, Sewarcberg J, Rhee MS, Cheng AK.~~ Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV type 1-infected patients: week 48 results. *J. Infect. Dis.* 2013; 208-:32-39.

Kakuda TN, Opsomer M, Timmers M, Iterbeke K, Van De Casteele T, Hillewaert V, **et al.** ~~Petrovic R, Hoetelmans RMW.~~ Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. *J. Clin. Pharmacol.* 2009; 54:949-957.

Lalezari J, McCallister S, Gigliotti M, Cohen C, Elion R, **Brinson C,** et al. Safety and efficacy study of bevirimat (BVM) in heavily treatment experienced HIV+ patients identifies the target phase 3 study profile. ICAAC. 2008; Abstract: H891.

Martin DE, Blum R, Wilton J, Doto J, Galbraith H, **Burgess GL**, et al. Safety and pharmacokinetics of bevirimat (PA-457), a novel inhibitor of human immunodeficiency

virus maturation, in healthy volunteers. *Antimicrobial Agents and Chemotherapy.* 2007(b);Sep:3063-6.

Appendix 1 Abbreviations

Rationale for Change

The abbreviations used in the document are added to the list of abbreviations.

AIDS	~~Auto~~ Acquired immunodeficiency syndrome
BID	**Twice daily**
DDI	**Drug-Drug Interaction**
PPD	**Pharmaceutical Product Development**
QD	**Once daily**
RIBA	**Recombinant Immuno-Blot Assay**
~~t1/2~~**t½**	Terminal elimination half-life

12.10.2. AMENDMENT 2

Protocol Amendment 2 (24-MAY-2017) from the Protocol Amendment 1 (26-Apr-2017)

Where the Amendment Applies

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

List of Specific Changes: (**bold** indicates text added and ~~strikethrough~~ indicates text removed)

Summary of Protocol Amendment Changes with Rationale

Amendment 2 includes expansion of the eligible subject population to allow treatment experienced HIV-1 infected patients, in addition to treatment naive patients. Patients with a treatment history of a prior maturation inhibitor will still be ineligible. Slight modifications were made to include flexible language for enrolment into Part B to allow prioritization of one dose cohort or to open randomization into Part B cohorts in a parallel fashion. Also the upper limit of the BMI inclusion criteria was increased from 31 to 35 kg/m^2.

Minor clarifications, re-numbering of sections and correction of typographical errors were also made throughout this amendment.

Author (s)

Rationale for change A minor correction was made to this section.

A minor correction was made to this section.

Revised Text

PPD PCPS, GSK, ~~Collegeville~~**Upper Providence**, PA, US

Title Page

Rationale for change

The protocol title was updated to reflect the new subject population, which is no longer limited to treatment naive patients.

Revised Text

A Phase 2a, Multicenter, Randomized, Adaptive, Open-label, Dose Ranging Study to Evaluate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Cobicistat-boosted GSK2838232 Monotherapy Over 10 Days in HIV-1 Infected ~~Treatment-Naive~~ Adults

Synopsis

Rationale

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed). The reference to a parallel enrolment design for Part B was also removed to allow for prioritizing enrolment into any one dose cohort based on emerging data from Part A.

Revised Text

Second paragraph

Three clinical studies of GSK2838232 (n=53 healthy subjects) have been completed thus far. One study (Study 204953) ~~is on-going~~**completed at the end of 2016 and analysis of the data is ongoing**. Healthy subjects have received GSK2838232 or placebo in single or repeated dose designs, to a maximum single dose of 250 mg or repeated dose (for 11 days) of 200 mg QD, in combination with ritonavir (RTV).

Fifth paragraph

Study 204953 ~~is an on-going study and continues the~~**investigated the safety and PK of GSK2838232 in** single and repeat-dose**s** ~~exploration of safety and PK of GSK2838232~~as well as the suitability of a new, capsule formulation. Doses of up to 250 mg GSK2838232/100 mg RTV (as single doses) or 200 mg GSK2838232/100 mg RTV (QD for 11 days) were studied. ~~As of 26 October 2016, the study is ongoing with a cohort of subjects due to receive~~**The final cohort of the study assessed** unboosted GSK2838232 (200mg BID) for 11 days. **The study completed at the end of 2016 and the data analysis is ongoing.**

Seventh paragraph

The objective of Study 200911 is to understand the safety, PK and HIV antiviral profile of GSK2838232/cobicistat (GSK2838232/cobi) when given to HIV-infected, treatment naive, otherwise healthy adults. Approximately 10 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology, and PK data analysis, approximately 8 subjects will be enrolled in each of between two and four Cohorts in Part B~~, which will be a parallel group design~~.

Design, Treatment Arms and Duration

Rationale for change

This section was updated to reflect the new subject population, which is no longer limited to treatment naive patients.The reference to a parallel enrolment design for Part B was also removed to allow for prioritizing enrolment into any one dose cohort based on

emerging data from Part A. A reference to Study 205820 was also included as data from this planned study will provide additional information on unboosted GSK2838232.

Revised Text

First paragraph

Approximately 34 HIV-1 infected ~~treatment-naive~~ subjects will be enrolled overall.

Second paragraph

This study is a 10-day monotherapy, open-label, adaptive, dose ranging, repeat-dose study and will be conducted as two parts with an interim (go/no-go) analysis performed after Part A (Table 1). Part A, Cohort 1 will evaluate a safe and well-tolerated dose level of GSK2838232 that has been tested (with RTV) in prior Phase I studies and that targets a high inhibitory quotient (IQ) value. Following the completion of an interim analysis of those data and according to criteria defined later in the protocol, further cohorts of 8 subjects will then be studied in Part B in ~~a parallel design in~~ two or more cohorts (depending upon the data obtained in Part A).

Table 1 Study Design for 200911

	Part A: GSK2838232/cobi Once Daily x 10 days[1]		Part B: GSK2838232/cobi Once Daily x 10 days[1,2]		
Cohort	N	232 Dose (mg)	Cohort	N	232 Dose (mg)
1	10	100			
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B~~, which are planned to run in a parallel, randomized fashion~~. All doses will be given with 150 mg cobicistat.
2. Part B GSK2838232 doses are an illustration of the projected doses per cohort. The actual doses for each cohort **and number of cohorts** are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobi co-dosing) may be added (the maximum dose in Part B would **likely** not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] was lower in HIV infected subjects than in healthy subjects at the same dose level).

Fourth paragraph

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) was assessed **and Study 205820, which plans to evaluate GSK2838232 at a dose of 500mg once daily (QD)**.

Section 2.2.2.1 Clinical Summary of Safety

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed).

Revised Text

Fifth paragraph

In ~~ongoing~~Study 204953, there have been a small number of CV-related events of any sort: There have been no serious adverse drug reactions, and no clinically significant drug-related abnormal findings for 12-lead ECGs, vital signs, safety laboratory results (including cardiac troponin I), or telemetry. The following cardiovascular AEs were observed during the course of the study but were not considered to be caused by GSK2838232 exposure

Section 2.2.2.2 Study 204953 (completed); Pharmacokinetic Data

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed and analysis is ongoing).

Revised Text

Second paragraph

In addition, it evaluated the relative bioavailability of a single fasted dose of micronized API powder blend in capsules with RTV compared to powder-in-bottle for oral suspension with RTV and the effect of a normal fat meal on the bioavailability of a single dose of GSK2838232 in the capsule formulation with RTV. It will evaluate GSK2838232 exposure after repeated doses of unboosted GSK2838232 in the capsule formulation. Noncompartmental PK analysis was performed using scheduled sample times. ~~This~~**The** ~~study is~~**anaylsis of data from this study is** ongoing; preliminary results are presented.

Section 4.1 Overall Design

Rationale for change

This section was updated to reflect the new subject population, which is no longer limited to treatment naive patients.The reference to a parallel enrolment design for Part B was also removed to allow for prioritizing enrolment into any one dose cohort based on emerging data from Part A.

Revised Text

First paragraph

This is a Phase IIa, multicenter, open-label, adaptive dose ranging, study to evaluate the antiviral effect, safety, tolerability, and PK of GSK2838232/cobi monotherapy over 10 days in ~~ART-naïve~~ HIV-1 infected adults who are not currently receiving ART therapy. Subjects who have received any ~~ART (including prior MI)~~ **prior maturation ihibitor** therapy will not be eligible for this study. To minimize the number of subjects exposed to suboptimal doses, an adaptive and dose ranging design is applied in this study.

Study Design for 200911

GSK2838232/cobi Once Daily for 10 days[1,2]					
Part A			**Part B**		
Cohort 1	**Dose (mg)**	**Interim Analysis**	**Cohort**	**N**	**(mg)**
N=10	100				
			2	8	200
			3	8	50
			4	8	20

1 . Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B~~, which are planned to run in a parallel, randomized fashion~~. All doses will be given with 150 mg cobicistat.

2 . Part B doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobicistat co-dosing) may be added. (The maximum dose in Cohort B will **likely** not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] is lower in HIV-infected subjects than in healthy subjects at the same dose level).

Day 1 – Day 10: Dosing

Second paragraph

Serial, intensive blood PK samples will be collected on Day 1 (up to 24 hours post-morning dose) and Day 10 (up to 96 hours post-morning dose), and limited, single blood PK samples pre-morning doses on Days 3 through 9, except for the weekend. Subjects will be required to fast for 10 hours [overnight] prior to the morning check in on the intensive PK sampling days (Days 1 and 10). All dosing days will require co-administration of treatment with a light snack/meal per cobicistat labeling guidelines. All doses of study medication will be taken with 240 mL of water. Subjects will be required to stay in the clinic on Days 1 and 10 until all specified assessments are completed (**8-**12 hours post-dose). Following Day 10, subjects will be required to attend the clinic for follow up assessments including virological and PK blood sampling for up to 3 weeks.

Section 4.2 Type and Number of Subjects

Rationale for change

Minor clarifications were made to this section.

Revised Text

At least 34 subjects will be enrolled such that approximately 6-10 evaluable subjects complete a number of cohorts. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels as appropriate.

If subjects prematurely discontinue the study, additional~~replacement~~ subjects may be ~~randomised~~**randomized** and assigned to the same treatment cohort at the discretion of the Sponsor in consultation with the Investigator.

Section 4.3 Design/Dose Justification

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed).

Revised Text

Last paragraph

There is no *a priori* intention to study GSK2838232 unboosted, unless: i) following the preliminary analysis of Part A Cohort 1, there is such pronounced antiviral activity that it would seem the estimates of projected IQ are low, in which case GSK2838232 may be evaluated in a subsequent cohort unboosted, or ii) the data from ongoing **and planned healthy volunteer trial**s,~~Cohort 7 in~~ Study 204953 (~~planned,~~ GSK2838232 200 mg BID **unboosted**) **and Study 205820 (GSK2838232 500mg QD** unboosted**)** support it.

Section 4.3.3 Interim Analysis

Rationale for change

Minor clarifications were made to this section to allow for flexibility around selecting dose cohorts for Part B based on emerging data from Part A.

Revised Text

An evaluation of GSK2838232 safety, efficacy and PK data will be done after Part A Cohort 1, if the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects and the Bayesian probability from Cohort 1 is less than 70%, the study will not move forward into Part B, otherwise doses will be selected for evaluation in Part B. If pharmacokinetic exposure after the 100 mg GSK2838232/cobi dose is in the range of values observed after 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower

(20 mg **and/or**~~,~~ 50 mg) and higher (200 mg) doses. The highest dose tested in Part B will be selected to result in exposures similar to those seen with 200 mg/r in Study 204953.

Section 4.4.3 Overall Benefit:Risk Conclusion

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed).

Revised Text

To date, **115**~~53~~ healthy subjects have received GSK2838232 in **four**~~three~~ completed studies. ~~One study (204953) is ongoing (52 healthy subjects have completed this study so far).~~

Section 5 SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Rationale for change

This section was updated to reflect the new subject population, which is no longer limited to treatment naive patients.The reference to a parallel enrolment design for Part B was also removed to allow for prioritizing enrolment into any one dose cohort based on emerging data from Part A.

Revised Text

Second paragraph

Approximately 10-12 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology and PK data analysis, approximately 8 subjects will be enrolled in each of Cohorts 2-4 in Part B~~, which will be a parallel group design~~. Eligible patients are those who are **maturation inhibitor**~~ART~~-naïve and who are not currently receiving ART therapy.

Last paragraph

If subjects prematurely discontinue the study, additional subjects may be enrolled ~~as replacement subjects and assigned to the same treatment at the discretion of the Sponsor~~.

Section 5.1 Inclusion Criteria

Rationale for change

The inclusion criteria were updated to reflect the new subject population, which is no longer limited to treatment naive patients. Also the upper limit of the BMI inclusion criteria was increased from 31 to 35 kg/m^2.

Revised Text

5. Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening. ~~No current and no prior ART. (A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug).~~

~~5.~~**6. Antiretroviral treatment naive or ART-experienced (maturation inhibitor naive). No current ART (last dose completed at least 6 weeks prior to the first dose of study drug).** ~~(~~A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug~~)~~.

~~6.~~7. Body weight ≥ 50 kg (110 lbs.) for men and ≥45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-3~~5~~1.0 kg/m^2 (inclusive)

Section 6.2 Treatment Assignment

Rationale for change

A minor clarification was made to this section.

Revised Text

Subjects will be assigned to treatment (active) **groups** in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Section 6.4 Blinding

Rationale for change

Minor clarifications were made to this section.

Revised Text

This will be an open-label study. Treatment allocation **and GSK2838232 dose levels** in Part B will be **determined after the analysis of Part A data.** ~~randomised (to GSK2838232 dose level).~~

12.10.3. AMENDMENT 3

Protocol Amendment 3 (15-JUN-2017) from the Protocol Amendment 2 (24-MAY-2017)

Where the Amendment Applies

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

List of Specific Changes: (**bold** indicates text added and ~~strikethrough~~ indicates text removed)

Summary of Protocol Amendment Changes with Rationale

Amendment 3 includes modification to the protocol Inclusion Criteria (#6) to ensure exclusion of treatment-experienced patients with limited remaining treatment options.

Section 5.1 Inclusion Criteria

Rationale for change

Additional language was added to the protocol Inclusion Criteria (#6) to clarify that with the patient population being expanded to include treatment-experienced patients for enrolment, patients with limited or no treatment options would remain ineligible.

Revised Text

6. Antiretroviral treatment naive or ART-experienced (maturation inhibitor naive). No current ART (last dose completed at least 6 weeks prior to the first dose of study drug). A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug. **NOTE: Subjects with limited therapeutic options, including but not limited to those who have failed ≥2 antiretroviral regimens for any reasons or have documented resistance to >2 classes of antiretrovirals or have interrupted their treatment due to resistance, will not be eligible.**

Section 7 Time and Events Table

Rationale for change

A modification was made to this section to clarify the days where site calls to IVRS would be made (Screen, Randomization, Early Termination and/or unscheduled visits only).

Revised Text

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Informed Consent	X																
Review inclusion/exclusion	X		X														
Demography including height, weight and BMI	X																
Brief physical			X														
Medical/medication/ drug/alcohol history	X		X														
CDC Classification	X		X													X	X
Prior antiretroviral therapy	X																
12-lead ECG[3]	X		X			X				X		X	X	X		X	X
Holter (24 hr)	X																
Vital signs[4]	X		X			X	X			X		X		X		X	X
Drug screen	X		X			X						X				X	
Hepatitis B Surface antigen and hepatitis C antibody testing	X																
Serum or urine β-hCG (WoCBP only)	X		X														X
Clinical lab tests (inc troponin)	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Fasting lipid panel	X																X
AE assessment[5]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Con Medication Review	X		X	X	X	X	X			X	X	X	X	X	X	X	X
HIV-1 RNA PCR[6]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Lymphocyte subsets[7]	X		X										X				
Plasma for genotype/phenotype[8]			X			X	X			X			X			X	X
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		X[14]
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														
Telephone call to IVRS[13]	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Plasma for storage[15]			X	X	X	X	X			X	X	X	X	X	X	X	X
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase 2a, Multicenter, Randomized, Adaptive, Open-label, Dose Ranging Study to Evaluate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Cobicistat-boosted GSK2838232 Monotherapy Over 10 Days in HIV-1 Infected Adults

Compound Number: GSK2838232

Development Phase: IIA

Effective Date: 24-MAY-2017

Protocol Amendment Number: 02

Author (s):

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CPMS, GSK, RTP, NC, US
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Clinical Pharmacology, ViiV Healthcare, RTP, NC, US
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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N227852_00	2016-NOV-09	Original
2015N227852_01	2017-APR-26	Amendment No. 1
Amendment 1 includes minor updates to Inclusion-Exclusion (IE) criteria, including clarification on use of pre- or post-exposure prophylaxis, and removal of exclusionary requirements related to concomitant medications and tobacco and alcohol use during the study. Guidance around relevant habits is included in the Lifestyle section of the protocol and adjustments were made to reduce restrictions on these requirements. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirements. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Furthermore, the serial ECG collection (up to 6h post-dose) was removed on Day 5. Finally, the post-study care guidance was updated to include an option for subjects to receive reimbursement for marketed ART for a limited period after completion of study treatment and follow up. Minor clarifications, reformatting of tables, re-numbering of sections and correction of typographical errors were also made throughout this amendment.		
2015N227852_02	2017-MAY-24	Amendment No. 2
Amendment 2 includes expansion of the eligible subject population to allow treatment experienced HIV-1 infected patients, in addition to treatment naive patients. Patients with a treatment history of a prior maturation inhibitor will still be ineligible. Slight modifications were made to include flexible language for enrolment into Part B to allow prioritization of one dose cohort or to open randomization into Part B cohorts in a parallel fashion. Also the upper limit of the BMI inclusion criteria was increased from 31 to 35 kg/m^2.		

SPONSOR SIGNATORY

PPD

May 24, 2017

Brian Johns, PhPPD Date

Vice President, HIV DPU

PPD

PPD

May 24, 2017

PPD Etienne Dumont, MD Date

Project Physician Lead

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor/SAE contact information	Pharmaceutical Product Development (PPD) Safety Hotline	PPD			PPD, 929 North Front Street, Wilmington, NC 28401
Secondary Medical Monitor	PPD MD				GlaxoSmithKline 1250 St Collegeville Rd Collegeville, PA 19426

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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): 116,094

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200911

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

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 200911

Rationale

GSK2838232 is a novel human immunodeficiency virus (HIV-1) maturation inhibitor that is being developed for the treatment of HIV-1 in combination with other antiretrovirals.

Three clinical studies of GSK2838232 (n=53 healthy subjects) have been completed thus far. One study (Study 204953) completed at the end of 2016 and analysis of the data is ongoing. Healthy subjects have received GSK2838232 or placebo in single or repeated dose designs, to a maximum single dose of 250 mg or repeated dose (for 11 days) of 200 mg QD, in combination with ritonavir (RTV).

Study HMI116787 (completed November 2013) was the First Time in Human study of GSK2838232 and assessed safety and tolerability of escalating doses (5 mg to 100 mg), food effect, and the impact of steady-state ritonavir on GSK2838232 pharmacokinetics (PK). Following successful completion of 3-month toxicology studies in rat and dog in 2014, clinical studies 200912 and 200207 were initiated. These were double-blind, placebo-controlled, single (Study 200912) and repeat-dose (Study 200207) escalation studies to investigate the safety, tolerability, and PK of GSK2838232 alone and when co-administered with ritonavir 100 mg once daily (QD) for 8-11 days. Further assessment of an alternative formulation was also an objective in Study 200912.

Both studies were prematurely terminated/completed in March/April 2015 because of concerns over cardiovascular (CV) toxicity, in particular a clinical CV serious adverse event (SAE) whereby the Food and Drug Administrating (FDA) imposed a clinical hold. Following submission of long-term (6-month rat, 9-month dog) chronic toxicology data and follow up to the clinical SAE in November 2015, the hold was released in January 2016 and Study 204953 was initiated.

Study 204953 investigated the safety and PK of GSK2838232 in single and repeat-doses as well as the suitability of a new, capsule formulation. Doses of up to 250 mg GSK2838232/100 mg RTV (as single doses) or 200 mg GSK2838232/100 mg RTV (QD for 11 days) were studied. The final cohort of the study assessed unboosted GSK2838232 (200mg BID) for 11 days. The study completed at the end of 2016 and the data analys is ongoing.

These studies have shown GSK2838232 with or without RTV to be well tolerated and, together with daily RTV dosing (“boosting”), demonstrate a PK profile suitable for progression to HIV patients in this Phase IIa proof of concept 10-day, monotherapy study design. However, potential concerns over protease resistance necessitate a change to a pharmacoenhancer without antiviral effects in this study of GSK2838232 monotherapy. Therefore, for Study 200911, cobicistat (Tybost,150 mg QD) will be substituted for RTV.

The objective of Study 200911 is to understand the safety, PK and HIV antiviral profile of GSK2838232/cobicistat (GSK2838232/cobi) when given to HIV-infected, treatment naive, otherwise healthy adults. Approximately 10 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology, and PK data analysis,

approximately 8 subjects will be enrolled in each of between two and four Cohorts in Part B.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate antiviral activity of GSK2838232/cobi in HIV-1 infected patients during 10 days of monotherapy.	• Change from baseline (Day 1) in plasma HIV-1 RNA
• To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days.	• Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments.
• To characterize the pharmacokinetics of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days.	• GSK2838232 PK parameters following dose administration, as follows: **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Secondary	
• To explore the relationship between GSK2838232 exposure and change in plasma HIV-1 RNA	• GSK2838232 PK parameters Day 10 AUC(0-τ), Cmax, Cτ with Day 11 HIV-1 RNA change from baseline
• To assess the immunologic effect of GSK2838232/cobi when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ cell count to Day 11
• To explore the relationship between GSK2838232 exposure and safety or immunologic parameters, if appropriate.	• GSK2838232 PK parameters on Day 10: AUC(0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count

Objectives	Endpoints
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate
• To estimate GSK2838232 accumulation and to assess attainment of steady state following administration of GSK2838232/cobi for 10 days in HIV infected subjects.	• **Accumulation:** GSK2838232 PK accumulation ratios (R): Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively • **Steady State:** pre-morning dose concentrations (C0) on Days 2 through 11
• To examine dose proportionality of GSK2838232 pharmacokinetic parameters following GSK2838232/cobi dosing for 10 days in HIV infected subjects.	• Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax, and Cτ at different dose levels for the assessment of dose proportionality
Note: Other exploratory objectives and endpoints will be specified in the RAP	

Design, Treatment Arms and Duration

Approximately 34 HIV-1 infected subjects will be enrolled overall.

This study is a 10-day monotherapy, open-label, adaptive, dose ranging, repeat-dose study and will be conducted as two parts with an interim (go/no-go) analysis performed after Part A (Table 1). Part A, Cohort 1 will evaluate a safe and well-tolerated dose level of GSK2838232 that has been tested (with RTV) in prior Phase I studies and that targets a high inhibitory quotient (IQ) value. Following the completion of an interim analysis of those data and according to criteria defined later in the protocol, further cohorts of 8 subjects will then be studied in Part B in two or more cohorts (depending upon the data obtained in Part A).

The totality of this data will provide a full dose-response of GSK2838232 over a wide dose range to explore the safety and PK/pharmacodynamics (PD) relationship of GSK2838232 in HIV-1 infected subjects and facilitate choice of doses for Phase IIb studies.

Table 1 Study Design for 200911

	Part A: GSK2838232/cobi Once Daily x 10 days[1]		Part B: GSK2838232/cobi Once Daily x 10 days[1,2]		
Cohort	N	232 Dose (mg)	Cohort	N	232 Dose (mg)
1	10	100			
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B. All doses will be given with 150 mg cobicistat.
2. Part B GSK2838232 doses are an illustration of the projected doses per cohort. The actual doses for each cohort and number of cohorts are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobi co-dosing) may be added (the maximum dose in Part B would likely not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] was lower in HIV infected subjects than in healthy subjects at the same dose level).

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) was assessed and Study 205820, which plans to evaluate GSK2838232 at a dose of 500mg once daily (QD).

Subjects in both parts will have a screening visit within 30 days prior to first dose and a follow-up visit 7-14 days after the last dose. Maximum duration of study participation will be approximately 6 weeks.

HIV Drug Resistance: Following cessation of GSK2838232/cobi dosing for 10 days, there will be prolonged exposure to waning plasma concentrations of GSK2838232, because of the long t½ (i.e., in the "tail" of the PK profile). However, based on in vitro resistance passage data with GSK2838232 [and unlike with many other ARV therapies], there appears to be a limited likelihood of developing maturation resistance mutations in HIV-infected subjects due to its virologic profile.

Analysis

The primary objectives of this study are to investigate the safety, tolerability, PK and antiviral activity of 10 days repeated doses of GSK2838232/cobi in HIV-1 infected otherwise healthy subjects. Descriptive summaries will be provided for safety, PK, and HIV viral load data.

2. INTRODUCTION

GSK2838232 is a novel human immunodeficiency virus (HIV)-1 maturation inhibitor (MI) that is being developed for the treatment of HIV-1 infection in combination with other antiretrovirals (ART).

2.1. Study Rationale

This 'proof of concept (PoC)' open-label study is being conducted to characterize the acute antiviral activity, pharmacokinetics (PK), the relationship between PK and antiviral activity, and safety of GSK2838232 given with 150 mg once daily (QD) cobicistat (GSK283232/cobi), administered across a range of doses over 10 days in HIV-1 infected patients. A two-part adaptive and dose ranging design is to be applied in this study. Data from this study will be utilized to select doses for further studies in Phase IIb.

2.2. Brief Background

Combination antiviral therapy with inhibitors of HIV protease, integrase, entry and reverse transcriptase (RT) has demonstrated significant improvement in acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality over the last 10-15 years. Emerging multi-class drug resistant viral strains and long-term toxicities warrant development of new classes of antiretroviral therapies targeting various parts of the HIV-1 viral life cycle [Wainburg, 2010]. The inhibition of maturation of HIV-1 is a novel target for drug development, distinct from viral protease RT or integrase [Saxena, 2012; Qian, 2009]. HIV maturation is the final cleavage step of the capsidSp1 (transcription factor) polyprotein that generates the functional capsid p24 protein. This mechanism of action results in accumulation of the uncleaved p25 protein with subsequent improper assembly of the HIV core, resulting in a non-infectious virion. Gel-based mechanism of action studies suggest that compound GSK2838232 acts as a maturation inhibitor. Western Blot analysis shows inhibition of capsid-Sp1 cleavage and accumulation of p25 in the presence of GSK2838232.

Prior validation of this target was demonstrated with the HIV maturation inhibitor known as bevirimat (BVM; [Martin, 2007a; Martin, 2007b; Martin, 2008; NORVIR, 2013]). BVM reached Phase II studies in HIV patients; however, only modest reductions in plasma HIV-1 ribonucleic acid (RNA) concentrations were observed in Phase IIa monotherapy studies [Mahmood, 2006; Martin, 2007] and a pattern of polymorphic (differential) antiviral activity [Wainburg, 2010] led to termination of BVM development. The average decrease from baseline to Day 14 plasma HIV-1 ribonucleic acid (RNA) was 0.54 and 0.70 log10 copies/mL for 200 mg and 300 mg twice daily regimens (Table 2); all subjects achieved plasma BVM concentrations above the in vitro EC90. Responders, classified based on 5 polymorphisms in HIV-1 gag (at positions 369, 370, and 371), achieved an average 1.15 log10 copies/mL reduction in plasma HIV-1 RNA, while an average 0.17 log10 copies/mL reduction was achieved for non-responders.

Table 2 Summary of Bevirimat Antiviral Response and PK in a 14-day Monotherapy Study in HIV-infected Adults

BVM dosage regimen	Mean (SD) viral load change from baseline to Day 14	[2]IQ	Plasma BVM [1]Cmin (μg/mL)	Plasma BVM [1]Cmax (μg/mL)	Plasma BVM [1]AUC(0-τ) (μg.h/mL)
200 mg BID (N=14)	-0.54 (0.64)	1.70	46 (41, 51)	58 (53, 64)	632 (571, 699)
300 mg BID (N=18)	-0.70 (0.77)	2.67	72 (65, 80)	91 (84, 99)	973 (890, 1064)

1. Cmin, Cmax, and AUC reported as geometric mean (95% CI).
2. IQ=geometric mean Cmin/in vitro EC90; reported EC90=27 μg/mL; all subjects achieved IQ ≥1.

AUC(0-τ) = Area under the concentration-time curve over the dosing interval; BVM = Bevirimat; CI = Confidence interval; Cmax = Maximum plasma concentration; Cmin = Minimum plasma concentration; EC90 = 50% protection against resistant mutant HIV infection; IQ = Inhibitory quotient; SD = Standard deviation.

Early clinical data for BMS955176, a second generation maturation inhibitor, have been recently presented [Nowicka-Sans, 2015]. In a 10-day monotherapy trial in HIV-infected patients, plasma HIV-1 RNA was reduced at doses of between 40 mg and 120 mg QD. All doses were well tolerated. The maximum change, seen between 10 and 12 days after starting dosing, was about 1.5 log10, which is substantially better than the effect demonstrated with BVM and may indicate the maximum expected clinical effect of inhibiting this viral target.

Although BMS955176 is currently in Phase II studies in HIV-infected patients, there are no maturation inhibitors approved for the treatment of HIV infection. The uncertainties of early drug development and continuing need for novel ART, especially for heavily treated/experienced HIV-infected persons, support continued compound development. GSK2838232's low nanomolar in vitro potency against multiple HIV-1 gag polymorphisms and broader spectrum across multiple HIV-1 subtypes indicates it has utility in this setting.

2.2.1. Preclinical Summary

Nonclinical pharmacology

Virology

GSK2838232, in vitro, is an inhibitor of HIV maturation by preventing the cleavage of the HIV gag structural subunit p25 to p24. GSK2838232 is a potent antiviral agent with a mean 50% maximal inhibitory concentration (50% maximal inhibitory concentration [IC50]) value of 1.6 nM (range: 0.8 to 4.3 nM) when tested in a panel of 26 HIV-1 isolates with various polymorphic gag genotypes in peripheral blood mononuclear cells (PBMCs), suggesting that GSK2838232 can inhibit a broad spectrum of HIV isolates. In another PBMC assay, GSK2838232 showed potent antiviral activity in 59 of 60 isolates with IC50 values ranging from 0.22 to 5.1 nM. GSK2838232 also inhibited HIV-1 strains containing the consensus Sp1 QVT region or the V370A polymorphism in MT4 cells (IC50 = 0.73 to 0.81 nM).

In an MT2 cell-based assay utilizing recombinant viruses harboring gag and protease from subjects before and after a protease inhibitor (PI) based regimen, GSK2838232 inhibited 12 of 15 viruses with a mean IC50 value of 1.7 nM (range = 0.4 to 3 nM). The remaining 3 viruses were not inhibited by GSK2838232 up to the top concentrations tested at 400 nM. There was no correlation of PI sensitivity and susceptibility to GSK2838232. GSK2838232 resistance mutations were selected for by serial passage of virus in a SupT1 cell-based assay with increasing concentrations of GSK2838232. In the lab strain NL4-3 and gag/protease recombinant viruses, the resistance mutation A364V arose and resistance confirmed by site-directed mutagenesis. This resistance mutation maintains susceptibility to other classes of anti-retrovirals including PIs and non-nucleoside RT inhibitors.

GSK2838232 was tested in vitro in combination with two marketed PIs, atazanavir and darunavir. Using a dose-wise additivity model, GSK2838232A showed additive anti-viral activity with both PIs.

Secondary Pharmacology

In a secondary pharmacology study, GSK2838232 was tested against a panel of receptors, ion channels and transporters and demonstrated no significant effect (IC50 of ≤1 μM). It is important to note that the selectivity for antiviral activity of GSK2828232 compared to all tested off-target activities was >100-fold, and the potential for organ toxicity was characterized in the nonclinical toxicology studies (see below).

In safety pharmacology studies in male rats, there were no hemodynamic changes or neurobehavioral effects following single oral doses up to 300 mg/kg. A single oral dose of GSK2838232 at 30 mg/kg or 300 mg/kg produced reversible increases in respiratory tidal volume (32% and 36%, respectively) and derived minute volume (17% and 26%, respectively) at 6 hours after dosing. These doses did not produce any effect on respiratory rate, airway resistance or body temperature. There were no respiratory effects in rats given 5 mg/kg (mean maximum plasma concentration [C_{max}] 0.12 μg/mL; AUC_{0-24} 1.0 μg.h/mL based on Day 1 of the 4-week repeat dose study). These findings were not considered to suggest a safety concern in humans.

GSK2838232 at the maximum feasible concentration, limited by solubility, of 4.09 μM (3.31 μg/mL) caused no inhibition of human ether-a-gogo related gene (hERG) tail current in Human Embryonic Kidney 293 cells stably transfected with hERG cDNA, indicating a low probability for interaction at the hERG channel.

In conscious telemetered male dogs (n=4), a single oral dose of GSK2838232 at 60 mg/kg (C_{max} 0.59 μg/mL; AUC_{0-24} 8.7 μg.h/mL based on Day 1 exposure data from the 4-week oral repeat dose toxicity study) was associated with one episode of non-sustained ventricular tachycardia in one dog lasting ~1.2 seconds. There were no effects on arterial pressures, heart rate, or electrocardiogram (ECG) interval durations. An investigative safety pharmacology cardiovascular study was conducted in telemetered dogs given 60 mg/kg/day for 4 weeks with serial monitoring by echocardiography, cardiac biomarkers, qualitative and quantitative electrocardiology, microscopy, and transmission electron microscopy (TEM) of the heart.

There were no changes in echocardiography endpoints, ECG intervals, ECG waveforms, arterial pressures, heart rates, serum cTpnI, N-terminal prohormone of brain natriuretic peptide (NTproBNP), or in heart tissue as assessed by TEM. With routine microscopy, one treated dog had a single focus of degeneration/necrosis of the tunica media (moderate) in an extramural artery and another treated dog had localised, mixed-cell inflammation (mild) along the epicardium of the coronary groove. Both changes have been reported in normal beagles and were considered of uncertain relationship to treatment in the absence of changes in any other structural or functional cardiovascular endpoints. The 28-day exposures were similar to the previous 4-week toxicity study in dogs: the C_{max} range at 60 mg/kg/day in this investigative safety pharmacology study was 0.542 to 2.00 µg/mL and range of AUC_{0-24} was 6.04 to 35.7 µg.h/mL. In subsequent repeat-dose studies in dogs treated for up to 9 months with up to 70 mg/kg/day, no changes were evident in cardiac biomarkers (including cTpnI and NTproBNP), functional (including ECG waveform) or structural (including microscopic evaluation) cardiovascular endpoints at slightly higher exposures than those achieved than in previous studies. The end of the 9-month study, gender averaged C_{max} at 70 mg/kg/day was 1.95 µg/mL and AUC_{0-24} was 38.8 µg.h/mL. These studies support an absence of GSK2838232-related functional or structural effects on the heart in preclinical testing. The No Observed Adverse Effect Level (NOAEL) was established at 20 mg/kg/day (on the basis of mild hepatic findings) with an associated area under the curve at 24 hours (AUC24) of 16.2 µg.hr/mL and Cmax 0.847 µg/mL.

Pharmacokinetics and product metabolism in animals

The PK of GSK2838232 were investigated in the mouse, rat, and dog. The oral bioavailability of GSK2838232 was low to moderate (~6% to 40%) depending on the species and formulation. Plasma and blood clearance were low and the volume of distribution at steady state was high relative to total body water. The half-life of GSK2838232 was short in the mouse and rat, but moderate in the dog. Systemic exposure of GSK2838232 generally increased in a less than dose-proportional manner. In rats, there were no differences in systemic exposure between single and repeat-dose administration, or between males and females. In a 7-day study in dogs, systemic exposures were generally similar between males and females and after single and repeat dosing; however, in a 4-week study, systemic exposures were higher in females than in males in the high-dose group (60 mg/kg/day) and higher after repeat dosing than after a single dose. The distribution of radioactivity in male pigmented rats following a single oral administration of [^{14}C] GSK2838232 at a target dose level of 20 mg/kg showed radioactivity was rapidly absorbed and widely distributed throughout the body with all tissues, except the brain and spinal cord. There were no tissues that retained detectable levels of radioactivity at 28 days post dose. In a bile duct canulated rat study, 30% of the administered dose was excreted in the bile as an acylglucuronide. In the same study, unchanged drug and metabolites were eliminated primarily in the bile and feces, while a mean of <1% of the dose was eliminated in urine.

In vitro, GSK2838232 is highly protein bound (>99.9%) and has low passive permeability. In vivo evidence suggests active uptake of GSK2838232 by transporters in the rat liver.

After single oral doses of 5, 100, or 300 mg/kg, the average liver to plasma ratio was 51, 17, and 10, respectively. After 7 days of dosing at 30, 100, or 300 mg/kg/day, liver to blood ratios ranged from 10 to 16.

In the 13-week repeat dose studies in dogs given 35 mg/kg BID (70 mg/kg/day), heart tissue collected at necropsy had GSK2838232 concentrations 2.5 to 5-times higher than the 24-hour post-dose plasma concentrations, similar to the previous 4-week CV investigative findings. In the 13-week repeat dose studies in rats given 300 mg/kg/day, heart tissue collected at necropsy had GSK2838232 concentrations approximately 3 times higher than the 24-hour post-dose plasma concentrations, similar to the previous 7-day findings. Overall GSK2838232 did not appear to be highly concentrated in heart tissue after repeat dosing and suggests that accumulation upon chronic dosing is unlikely.

Routes of metabolism identified in liver microsomal incubations and rat, dog, and human hepatocytes were N-dealkylation, oxidation, oxidative deamination, and glucuronidation, alone or in combination, with no human-specific metabolites detected. N-dealkylated products and glucuronidation were observed in rat plasma and the bile. In general, in vitro metabolite profiles of the nonclinical species and human were qualitatively similar, such that all metabolites of [^{14}C] GSK2838232 observed in human hepatocyte incubations were observed in rat and/or dog. Minor to trace levels of potential aldehydes metabolites formed as a result of N-dealkylation and oxidative deamination were observed in rat, dog and humans.

GSK2838232 did not show evidence for glutathione adduct formation in rat or human liver microsomes. Data from pooled human liver microsomes along with recombinant cytochrome P450 (CYP) enzymes suggest that in vitro the oxidative metabolism of GSK2838232 was primarily mediated by CYP3A4. Preliminary in vitro investigations showed GSK2838232 did not inhibit CYP1A2, 2C9, 2C19, 2D6, 3A4 and was not a metabolism-dependent inhibitor of CYP3A4. No drug interaction risk was identified for co-administrated substrates of UGT1A1, 1A3, 1A6, 1A9, 2B7, and 2B15, OAT1, OAT3, OATP1B1, OATP1B3 or OCT2 at a clinical dose of 200 mg GSK2838232/ritonavir (predicted Cmax 0.32 μM). Extrapolation of the clinical risk (using FDA and EMA regulatory guidance) did indicate a risk for GSK2838232-mediated inhibition of UGT1A4 and of gut contributions of CYP3A4, P-gp, and BCRP at the same clinical exposure; however, the potential for clinically significant interactions via these mechanisms is predicted to be low (<2 fold change in AUC). GSK2838232 did show weak induction of CYP3A4 enzyme activity. However, based on the maximum predicted plasma concentrations and high protein binding, the potential for clinically significant drug interactions through CYP3A4 induction by GSK2838232 appears to be low.

The inclusion of cobicistat as a CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is unlikely to produce a significantly different profile of GSK2838232 ADME (and therefore systemic exposure); however, there have been no preclinical studies conducted with GSK2838232 and cobicistat to date.

Toxicology

GSK2838232 administered by oral gavage in repeat dose studies up to 6 months duration resulted in no adverse treatment-related effects in rats given up to 300 mg/kg/day QD.

In dogs given up to 70 mg/kg/day (35 mg/kg/day BID), adverse liver effects were noted at this dose in the 9-month repeat dose study. Though isolated, low grade changes in heart rate and cardiac troponin I (cTnI) had been noted in 4-week toxicity studies in rats and dogs; however, there were no treatment-related structural or functional cardiovascular changes in studies of 3 months and greater duration as assessed by echocardiography, ECG, microscopy, and cardiac biomarkers, indicating an absence of GSK2838232-related functional or structural effects on the heart in preclinical testing.

Only non-adverse treatment-related changes were noted in the definitive 6-month rat study, which included occasional salivation in animals given 300mg/kg/day and minimal clinical pathology changes without histologic correlates (transient clinical chemistry changes at ≥5 mg/kg/day and reversible urine chemistry changes at 300 mg/kg/day). The NOAEL in this study was considered to be 300 mg/kg/day (mean AUC[0-t] 21.3 μg.h/mL, mean Cmax 1.77 μg/mL [Week 26 values for males and females combined]).

As noted above, dogs given GSK2838232 at 70 mg/kg/day for 9 months had minimal to moderate pigmentation (consistent with bile) with minimal to mild mixed cell infiltration in the liver and isolated mild increases in alanine aminotransferase (ALT) activity. These findings were considered adverse, but were reversible after the 6-week off-dose period. The NOAEL for this dog study was considered to be the mid-dose level of 20 mg/kg/day (mean AUC[0-t] 16.2 μg.h/mL, mean Cmax 0.847 μg/mL [Week 39 values for males and females combined]).

Data from genotoxicity assessments suggest that GSK2838232 does not present a genotoxic hazard to humans.

During discussions with the FDA regarding the resolution of the clinical hold, the Agency recommended that the sporadic cardiovascular changes observed in the early (1-month) rat GLP study at the highest dose level (300 mg/kg/day) should be considered when defining the NOAEL and establishing a safe dose of GlaxoSmithKline (GSK) for the initiation of this study protocol. Accordingly, for the initial PK studies, the reference dose level of 30 mg/kg/day in the 1-month rat study was initially used to define the NOAEL and therefore the values for fold cover at maximum projected mean exposure and Cmax in human subjects were lower, at >2.5-fold. However, based on the cumulative clinical safety data through Cohort 5 of Study 204953, the designated NOAEL for the most sensitive species (i.e., 20 mg/kg/day in the 9-month dog study based on liver endpoints) is currently used for assessing fold-cover for projected clinical dosing in this study**.**

The inclusion of cobicistat as a CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is unlikely to produce a significantly different profile of GSK2838232 ADME (and therefore systemic exposure and toxicity); however, there have been no preclinical studies conducted with GSK2838232 and cobicistat to date.

Full details of non-clinical and clinical data may be found in the current Investigator's Brochure (IB) [GSK Document Number 2012N151889_03].

2.2.2. Clinical Summary of Safety and Pharmacokinetics

To date, GSK2838232 has been evaluated in three completed clinical studies with or without ritonavir (RTV) (GSK2838232/r). A fourth study (204953) completed late 2016 and data analysis is ongoing. Full details of the clinical results can be found in the Investigator's Brochure.

2.2.2.1. Clinical Summary of Safety

As of November 2016 fifty-three subjects had been exposed to GSK2838232 in 3 completed studies. One study (204953) completed in late 2016 and the analysis of results are ongoing (63 subjects were exposed to GSK2838232/r or placebo so far in this study). Overall, drug-related adverse events have been few and mild, and included headache, dizziness, fatigue, nausea, and palpitations and anxiety. Similarly, treatment-emergent laboratory abnormalities have also been few and mostly grade 1. There have been no discernible patterns, thus far, in terms of AEs or laboratory abnormalities.

One subject in study 200912 discontinued treatment with RTV due to an AE. A 47-year-old female who developed right upper quadrant abdominal pain, nausea and flatulence associated with grade 4 elevations in ALT and aspartate aminotransferase, and grade 2 elevations in total bilirubin (BIL). She was diagnosed with a common bile duct obstruction due to gallstones that spontaneously resolved. The Investigator assessed this AE as unrelated to study treatment.

Due to sporadic CV-related safety signals in the early animal studies (see Section 2.2.2), intense CV monitoring was in place for all four studies.

One AE occurred in HMI116787 that was initially considered a CV AE but after further evaluation was considered not to be of cardiac etiology. Two CV AEs occurred in 200207 that were initially considered possibly related to GSK2838232 exposure. However, further evaluation confirmed that there is a low likelihood that these events were due to GSK2838232 exposure. A summary of each event is provided in the IB.

In Study 204953, there have been a small number of CV-related events of any sort: There have been no serious adverse drug reactions, and no clinically significant drug-related abnormal findings for 12-lead ECGs, vital signs, safety laboratory results (including cardiac troponin I), or telemetry. The following cardiovascular AEs were observed during the course of the study but were not considered to be caused by GSK2838232 exposure:

- In Part 1A (Cohort 1), Period 2, a subject was withdrawn due to an AE (low hemoglobin) prior to GSK2838232 exposure Day -2. A replacement subject was brought in, but was not dosed with GSK2838232 or placebo because during the 2-day RTV run-in, on Day -1, the replacement subject met the stopping criteria for telemetry due to as brief occurrence of asymptomatic, NSVT prior to the first dose of GSK2838232 or placebo. Because the subject was excluded from the study prior to the first dose of investigational drug, the NSVT was not considered to be a serious and unexpected adverse drug reaction that would qualify for IND safety reporting.

- In Part 1A (Cohort 1), Period 3 (Period "3A" for the purpose of differentiating between 100 mg GSK2838232/r vs. 200 mg GSK2838232/r), one subject was discontinued prior to the first dose of study drug due to a series of cardiovascular findings (pre-ventricular contractions on telemetry). None of the findings were abnormal or atypical, but the investigator determined that this would not be a good etiology to have in a subject about to receive investigational drug. Because the event occurred prior to first dose of investigational drug, the finding was not considered to be due to GSK2838232 exposure.
- In Part 1A (Cohort 1), Period 3 (Period "3A" for the purpose of differentiating between 100 mg GSK2838232/r vs. 200 mg GSK2838232/r), one subject who had already been dosed on 2 previous occasions (with either GSK2838232 or placebo) was dosed for 2 days with RTV, and then on 05 May 2016 was dosed with either GSK2838232/r or placebo/r as scheduled. On the following day (06 May 2016), the subject experienced an asymptomatic, 6-beat run of NSVT, which was classified at the time as an SAE. Further monitoring, including continuous Holter monitoring revealed no further events. The subject had no troponin elevation throughout the study. After additional investigation it was determined that the NSVT had occurred after the subject had received placebo the previous day. Although the subject had received active on the two prior visits, the protocol allowed for sufficient washout between each dose. Therefore, because the subject had received placebo prior to experiencing the NSVT, the event was not considered to be due to GSK2838232 exposure or a serious and unexpected suspected adverse reaction that would qualify for IND safety reporting.
- In Part 2 (Cohort 6, 200mg/r), a 40 year old male enrolled in the study with no significant medical history experienced an asymptomatic ventricular triplet (NSVT) while asleep at 5:33am on Day 8 (of 11 days worth of dosing) approximately 21 hours after receiving 200 mg GSK2838232/r on the previous day at 8.25am. This event was noted by the site staff and the subject was assessed and found to have no associated clinical symptoms or complaints. The GSK medical monitor was notified. Because the subject was not symptomatic and this did not meet protocol-defined stopping criteria, the study was not unblinded at the time, and the subject was allowed to continue dosing. Dosing in the study is now complete and no further events have been noted. It was the assessment of the site PI and the GSK safety/monitoring team that a ventricular triplet can be seen in healthy volunteers on continuous Holter monitoring. Therefore neither the PI nor GSK considered this event to be a serious and unexpected suspected adverse reaction.

2.2.2.2. Study 204953 (completed); Pharmacokinetic Data

Study 204953 investigated the safety, tolerability, and PK of escalating doses of GSK2838232 as micronized API, with 100 mg RTV, initially as single doses and then as repeated doses for 11 days.

In addition, it evaluated the relative bioavailability of a single fasted dose of micronized API powder blend in capsules with RTV compared to powder-in-bottle for oral suspension with RTV and the effect of a normal fat meal on the bioavailability of a single dose of GSK2838232 in the capsule formulation with RTV. It will evaluate GSK2838232 exposure after repeated doses of unboosted GSK2838232 in the capsule formulation. Noncompartmental PK analysis was performed using scheduled sample times. The anaylsis of data from this study is ongoing; preliminary results are presented.

Pharmacokinetic analysis was performed on GSK2838232 plasma concentration-time data using nominal time following single doses of 50, 100, and 250 mg in combination with RTV in Part 1A of Study 204953 (Table 3). On average, GSK2838232 Cmax values were reached 4-6 hours after dosing. Terminal half-life values ranged from 15 to 28 hours across the three dose levels. Overall, broad dose proportionality was observed for Cmax and AUC(0-∞) values with ascending single doses of GSK2838232 (50, 100, and 250 mg with 100 mg RTV).

Table 3 Summary of Preliminary Pharmacokinetic Parameter Values after Single Doses of GSK2838232 in Combination with 100 mg Ritonavir (Study 204953, Part 1A)

Dose (mg)	n	t½ (h)	tlag (h)	tmax (h)	Cmax (ng/mL)	AUC(0-∞) (ng.h/mL)
50	8	22.7 (17%) (17.2-28.5)	0.188 (138%) (0-0.5)	3.63 (41%) (2.5-6.0)	17.2 (43%) (8.7-27.9)	458.6 (33%) (210.6-662.0)
100	6	18.0 (14%) (15.8-22.3)	0.167 (155%) (0-0.5)	6.00 (59%) (2.5-12.0)	25.2 (20%) (17.5-31.5)	890.5 (20%) (619.1-1053)
250	5	17.3 (6.4%) (15.5-18.6)	0 (-) (0-0)	5.50 (71%) (2.0-12.0)	60.7 (23%) (40.8-73.1)	1731 (29%) (1222-2505)

Data are presented as mean (CV) (minimum-maximum).

Study 204953 Part 1B was an open label, 2x2+1 three-period, crossover design, evaluating the relative bioavailability of the micronized API GSK2838232 powder blend in capsules compared to the PiB reference formulation for the first two periods, with the assessment of food effect on the capsule formulation in Period 3.

The relative bioavailability of the micronized powder blend in 50 mg hand-filled capsules compared to the micronized API as PiB for oral suspension was assessed as 100 mg GSK2838232 single doses with 100 mg RTV after two pre-doses (48 h) in the fasted state in a randomized crossover design in 12 subjects in the first two periods of Part 1B of Study 204953. Preliminary geometric mean AUC(0-∞) and Cmax values were approximately 45% and 60% higher, respectively, after administration in the capsule formulation compared to oral suspension from PiB (Table 4).

Table 4 Preliminary Assessment of Relative Bioavailability of Capsule Formulation vs. Powder-in-Bottle Formulation of GSK2838232 (Study 204953, Part 1B)

Parameter	Test	Reference	n	Ratio of Geometric Least Square Means	90% CI of Ratio
AUC(0-∞)	Capsule	PiB	12	1.43	(1.194,1.702)
Cmax	Capsule	PiB	12	1.58	(1.312,1.900)

PiB = powder-in-bottle.

The potential food effect with the capsule formulation was assessed as 100 mg GSK2838232 single doses with 100 mg RTV after two pre-doses (48 h) in the fasted state and with a normal fat meal in a non-randomized crossover design (fasted in either Period 1 or 2, fed in Period 3). Eleven subjects provided data for both dietary conditions. Preliminary geometric mean AUC(0-∞) and Cmax values were approximately 60% higher after administration in the capsule formulation with a normal fat meal compared to the fasted state (Table 5).

Table 5 Preliminary Assessment of the Effect of a Normal Fat Meal on GSK2838232 Exposure when Administered as a Capsule Formulation with Ritonavir (Study 204953, Part 1B)

Parameter	n	Capsule – food Geometric mean	Capsule – fasted Geometric mean	Ratio of geometric means (food/fasted)
AUC(0-∞) (ng.h/mL)	11	2414	1539	1.57
Cmax (ng/mL)	11	76.9	47.2	1.63

Repeat dose PK parameter values in Study 204953 Part 2 were determined on Day 1 and Day 11 using nominal time in Part 2 of Study 204953 (Table 6). After the Day 11 dose of GSK2838232 with RTV, exposure (Cmax, AUC[0-τ]) appeared to increase proportionally with the increase in dose level with the PiB and capsule formulations.

Table 6 Summary of Preliminary Pharmacokinetic Parameter Values on Day 1 and Day 11 during Repeated Dosing of GSK2838232 in Combination with 100 mg Ritonavir (Study 204953, Part 2)

Dose (mg)	n	t½ (h)	tlag (h)	tmax (h)	Cmax (ng/mL)	AUC(0-τ) (ng.h/mL)	Cτ (ng/mL)
Study Day 1							
20 (PiB)	6	-	0.417 (49%) (0-0.5)	3.67 (11%) (3.0-4.0)	12.2 (47%) (5.8-20.8)	189.4 (40%) (83.7-284.4)	6.1 (39%) (2.5-8.9)
50 (PiB)	6	-	0.167 (155%) (0-0.5)	3.00 (51%) (2.0-6.0)	18.7 (40%) (9.0-25.9)	288.7 (39%) (138.6-380.2)	9.5 (35%) (5.1-12.6)
100 (capsules)	6	-	0.167 (155%) (0-0.5)	2.25 (23%) (1.5-3.0)	48.4 (32%) (28.1-69.6)	664.1 (31%) (422.5-932.7)	21.6 (33%) (12.8-29.3)
200 (capsules)	6	-	0.083 (245%) (0-0.5)	2.50 (25%) (2.0-3.5)	79.4 (38%) (50.8-125)	1124 (39%) (636.7-1794)	38.9 (36%) (21.7-58.6)
Study Day 11							
20 (PiB)	6	19.2 (16%) (15.1-24.2)	-	5.00 (32%) (2.5-6.0)	27.4 (38%) (11.3-40.4)	474.3 (31%) (214.3-613.2)	15.3 (30%) (7.1-19.2)
50 (PiB)	6	27.3 (52%) (15.2-50.4)	-	3.50 (46%) (1.5-6.0)	58.0 (24%) (40.9-78.0)	1113 (23%) (762.6-1459)	38.8 (29%) (24.5-51.7)
100 (capsules)	6	17.9 (18%) (15.2-23.7)	-	4.00 (40%) (2.5-6.0)	133 (23%) (94.7-164)	2492 (27%) (1624-3301)	81.7 (30%) (45.9-113)
200 (capsules)	6	-[1]	-	3.33 (45%) (1.5-6.0)	240 (38%) (127-368)	4389 (45%) (2095-7161)	151 (46%) (67.8-250)

Data are presented as mean (CV) (minimum-maximum).

1. Concentration data were available up to 24 h after the Day 11 dose, and t½ values were not calculated.

2.2.2.3. Overall Summary/Conclusions of PK data

The original formulation used in the first three studies with GSK2838232 (HMI116787, 200207, and 200912) was SDD. Data from Study 200912 demonstrated that a change to the API formulation of GSK2838232 was feasible for future clinical studies. Study 204953 utilized micronized API powder in a bottle as well as in a capsule. The capsule was shown to be a viable solid dosage form for subsequent studies. A more detailed summary of the data from Study 204953 is in Section 2.2.2.2.

- GSK2838232 SDD did not overall demonstrate significant escalation in exposure from an increase in dose from 100 mg to 200 mg in a cross-study comparison. The API PiB formulation showed a proportional increase in AUC and Cmax for a 2-fold dose escalation from 100 mg to 200 mg.
- The observed tmax of the API form was significantly increased over the SDD formulation (the API formulation also increased tlag relative to SDD).
- The bioavailability of the GSK2838232 API formulation was on average 30-50% of the bioavailability of SDD formulation, but there was a large observed range of relative intra-subject exposures (11-150%).
- Both 10 mg SDD and 20 mg API showed a 10-fold or greater increase in AUC with steady-state RTV (100 mg QD for 10 days) with a smaller (≤4-fold) increase in observed Cmax. The t½ of GSK2838232 increased from 15-18 hours to 34-42 hours in the presence of steady-state RTV, regardless of formulation.
- After single doses of 50 to 250 mg GSK2838232 with RTV, increases in Cmax and AUC(0-∞) values were broadly proportional to the increase in dose. On Day 11 after repeated daily 20 to 200 mg doses of GSK2838232 with RTV, increases in Cmax and AUC(0-τ) values appeared to be proportional to the increase in dose with the PiB and capsule formulations.
- The relative bioavailability of the micronized API powder blend in capsules with RTV was approximately 45%-60% higher than the bioavailability of the micronized API administered as oral suspension from PiB with RTV.
- Co-administration of the micronized API powder blend in capsules with RTV and a normal fat meal resulted in an approximately 60% increase in geometric mean Cmax and AUC(0-∞) values compared to the fasted state with RTV (Study 204953).
- Variability remains fairly constant across formulations and boosted versus unboosted at around 30%-40% (moderate-high).
- Projections of potential future efficacious boosted GSK2838232 API regimens suggest that doses of 20 to 200 mg GSK2838232 API co-administered with RTV will result in mean trough values of at least 3-fold above the derived 90% maximal inhibitory concentration (IC90) target value (5 ng/mL). Even if protein binding has more impact than envisaged and causes a 5-fold increase in IC90 as seen in some preclinical virology studies, the predicted troughs will still be significantly higher than the 5-fold shifted IC90 (25 ng/mL) at doses of 50 mg or higher with RTV.
- The average and maximum AUC/Cmax values observed at the maximum dose studied to date are below NOAEL values in preclinical chronic toxicology studies (6-month rat, 9-month dog).

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To evaluate antiviral activity of GSK2838232/cobi in HIV-1 infected patients during 10-days of monotherapy.	• Maximum decline from baseline (Day 1) in plasma HIV-1 RNA
• To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days.	• Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments.
• To characterize pharmacokinetics (PK) of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days	• GSK2838232 PK parameters following dose administration, as follows: **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Secondary	
• To explore the relationship between GSK2838232 exposure and change in plasma HIV-1 RNA	• GSK2838232 PK parameters Day 10 AUC(0-τ), Cmax, Cτ with Day 11 HIV-1 RNA change from baseline
• To assess the immunologic effect of GSK2838232/cobi when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ cell count to Day 11
• To explore the relationship between GSK2838232 exposure and safety or immunologic parameters, if appropriate.	• GSK2838232 PK parameters on Day 10: AUC(0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate

Objectives	Endpoints
• To estimate GSK2838232 accumulation and to assess attainment of steady state following administration of GSK2838232/cobi for 10 days in HIV infected subjects.	• **Accumulation:** GSK2838232 PK accumulation ratios (R): Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively • **Steady State:** pre-morning dose concentrations (C0) on Day 2 through 11
• To examine dose proportionality of GSK2838232 PK parameters following GSK2838232/cobi dosing for 10 days in HIV infected subjects.	• Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax and Cτ at different doses levels for the assessment of dose proportionality
Note: Other exploratory objectives and endpoints will be specified in the RAP	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIa, multicenter, open-label, adaptive dose ranging, study to evaluate the antiviral effect, safety, tolerability, and PK of GSK2838232/cobi monotherapy over 10 days in HIV-1 infected adults who are not currently receiving ART therapy. Subjects who have received any prior maturation ihibitor therapy will not be eligible for this study. To minimize the number of subjects exposed to suboptimal doses, an adaptive and dose ranging design is applied in this study.

This study consists of a screening visit, a 10-day treatment period, and follow-up evaluations for 2 weeks following last dose.

Screening will be performed as the patients are identified, within 30 days of the first dose of study drug. Eligible HIV-1 infected subjects will receive study treatments for 10 days.

Table 7 Study Design for 200911

GSK2838232/cobi Once Daily for 10 days[1,2]					
Part A			**Part B**		
Cohort 1	**Dose (mg)**	**Interim Analysis**	**Cohort**	**N**	**(mg)**
N=10	100				
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B. All doses will be given with 150 mg cobicistat.
2. Part B doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobicistat co-dosing) may be added. (The maximum dose in Cohort B will likely not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] is lower in HIV-infected subjects than in healthy subjects at the same dose level).

After successfully completing screening evaluations, the first cohort will enroll 10 subjects to receive the 100 mg GSK2838232/cobi dose. Following interim analysis of Cohort 1, if warranted, Cohorts 2-4 will each enroll 8 subjects to receive a range of GSK2838232/cobi doses.

Day 1 – Day 10: Dosing

Subjects will report to the clinic for outpatient visits in the morning on Days 1 through 10 during the treatment period, except for the weekend (Days 6 and 7). Subjects will arrive each day prior to administration of the morning dose for safety and lab assessments, including HIV-1 RNA blood draws, as described in the Time and Events Table (Section 7.1). Subjects will begin receiving study drug in the morning of Day 1.

Serial, intensive blood PK samples will be collected on Day 1 (up to 24 hours post-morning dose) and Day 10 (up to 96 hours post-morning dose), and limited, single blood PK samples pre-morning doses on Days 3 through 9, except for the weekend. Subjects will be required to fast for 10 hours [overnight] prior to the morning check in on the intensive PK sampling days (Days 1 and 10). All dosing days will require co-administration of treatment with a light snack/meal per cobicistat labeling guidelines. All doses of study medication will be taken with 240 mL of water. Subjects will be required to stay in the clinic on Days 1 and 10 until all specified assessments are completed (8-12 hours post-dose). Following Day 10, subjects will be required to attend the clinic for follow up assessments including virological and PK blood sampling for up to 3 weeks.

Subjects will be given morning doses on Days 1 through 10 (except for the weekend) in the clinic. Weekend morning doses (Days 6 and 7) will be packaged and sent home for self-administration. After Day 11, the subjects will return frequently for assessments including blood draws for PK and HIV viral load. A diary card will be used to monitor dosing adherence.

Follow-up Visits:

Subjects will return to the clinic on Days 11, 12, 14 (±1 day), and 21 (±1 day) for PK and measurement of HIV-1 RNA levels, viral genotype/phenotype and safety assessments as shown in the Time and Events Table (Section 7.1).

4.2. Type and Number of Subjects

At least 34 subjects will be enrolled such that approximately 6-10 evaluable subjects complete a number of cohorts. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels as appropriate.

If subjects prematurely discontinue the study, additional subjects may be randomized and assigned to the same treatment cohort at the discretion of the Sponsor in consultation with the Investigator.

4.3. Design/Dose Justification

The fastest track to establishing antiviral potential of any novel HIV drug is to study a short course of monotherapy in HIV infected subjects. There is precedent for this across a number of classes of ART drugs.

Uncertainties over the impact of protein binding on the activity of GSK2838232 and the inherent potency of inhibiting the HIV maturation process as a target remain key objectives for the GSK2838232 program. This two-part adaptive design will allow an early understanding of the potential of GSK2838232 in combination with cobicistat (and by implication, RTV), while not exposing HIV-infected subjects to longer courses of what may be suboptimal doses and possible development of resistance.

Early clinical studies have indicated that in order to achieve reasonable IQ values likely to be associated with antiviral efficacy, GSK2838232 will need to be boosted with a pharmacoenhancer, such as RTV or cobicistat (in common with many CYP3A4 substrates).

There is no *a priori* intention to study GSK2838232 unboosted, unless: i) following the preliminary analysis of Part A Cohort 1, there is such pronounced antiviral activity that it would seem the estimates of projected IQ are low, in which case GSK2838232 may be evaluated in a subsequent cohort unboosted, or ii) the data from ongoing and planned healthy volunteer trials,Study 204953 (GSK2838232 200 mg BID unboosted) and Study 205820 (GSK2838232 500mg QD unboosted) support it.

4.3.1. GSK2838232 with Ritonavir

In Study HMI116787, a single dose of 10 mg GSK2838232 (SDD) given after 10 days of RTV 100 mg daily dosing (to steady state) demonstrated an increase in overall exposure (AUC) and Cmax by an average of 10.8- and 2.6-fold, respectively, compared to 10 mg GSK2838232 alone. Terminal phase half-life also increased from approximately 20 hours to 34 hours. This effect was presumably the result of an inhibition of a CYP3A4-mediated pathway. Studies 200912 and 200207 also indicated the utility of RTV in boosting GSK2838232 concentrations.

These data indicate the viability of studying a number of GSK2838232+RTV regimens in this PoC study. Predicted exposures following different GSK2838232 doses with steady-state RTV are presented in Table 8, based on the results of linear regression analyses of the preliminary Day 11 data in Study 204953 (dose levels of 20 to 200 mg) and assuming no significant differences in PK (ADME) between HIV-infected subjects and healthy subjects.

Table 8 Predicted Mean Steady-State GSK2838232 AUC(0-24), Cmax, and IQ, Following Repeated Dose Administration + RTV with Fold Cover to NOAEL

Dose (mg)	Projected AUC24 (ng.h/mL)[1]	Fold cover to NOAEL Dog[2]	Projected Cmax (ng/mL)[1]	Fold cover to NOAEL Dog[2]	IQ[3]
20+RTV	451	36	24	35	3.1
50+ RTV	1127	14	61	14	7.7
100+ RTV	2253	7.2	122	6.9	15
150+RTV	3380	4.8	183	4.6	23
200+RTV	4506	3.6	244	3.5	31

1. Predicted mean values based on linear regression analyses of preliminary Day 11 data in Study 204953.
2. Lowest NOAEL, 20 mg/kg/day obtained from 9-month study in dogs (AUC24 16200 ng.h/mL and Cmax 847 ng/mL)
3. Mean IQs derived from predicted Cτ/IC90 (with target of 5 ng/mL).

Cτ = Pre-dose (trough) concentration at the end of the dosing interval, IQ= inhibitory quotient.

The IQ following 20 mg to 200 mg GSK2838232/r QD is predicted to be >3 to >30-fold above the minimal target value (5 ng/mL) which was derived from preclinical virological assessment as 4 × EC50. No protein binding adjustment has been made because there was a minimal (≤5 fold) shift in assays where the effect of protein was assessed. If protein binding has more impact than anticipated, it is possible that the target Cmin value is approximately 25 ng/mL. In that scenario, projected IQ values at 200 mg/r QD would still be >5.

4.3.2. GSK2838232 with Cobicistat

There have been no preclinical or clinical studies with GSK2838232 and cobicistat to date; however, a review of the literature indicates that pharmacoenhancement of drugs that are known to have dominant CYP3A metabolic pathways is similar with either RTV or cobicistat [Kakuda, 2009; Elion, 2011; Gallant, 2013]. Thus, the use of cobicistat as the CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is expected to produce a similar profile of GSK2838232 ADME (and therefore systemic exposure). The pharmacokinetic data available after Part A Cohort 1 will confirm this assumption.

4.3.3. Interim Analysis

An evaluation of GSK2838232 safety, efficacy and PK data will be done after Part A Cohort 1, if the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects and the Bayesian probability from Cohort 1 is less than 70%, the study will not move forward into Part B, otherwise doses will be selected for evaluation in Part B. If pharmacokinetic exposure after the 100 mg GSK2838232/cobi dose is in the range of values observed after 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower (20 mg and/or 50 mg) and higher (200 mg) doses. The highest dose tested in Part B will be selected to result in exposures similar to those seen with 200 mg/r in Study 204953.

4.4. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2838232 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.4.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2838232		
Cardiovascular	Pre-clinical studies have shown the following findings: elevated heart rates, an isolated episode of non-sustained ventricular tachycardia and minimal to mild, sporadic troponin I elevations in dogs. A subsequent investigative cardiovascular study in telemetered dogs treated for 4 weeks did not replicate these effects. Isolated microscopic cardiovascular changes were noted (focal extramural arteritis and localized epicardial inflammation), however these changes were considered of uncertain relationship to GSK2838232 because similar findings occur at low incidence in normal beagles and there were no GSK2838232-related functional changes by telemetry and echocardiography, or changes in cTpnI and NTproBNP. In addition there was no correlation between histologic changes and plasma exposure or heart tissue concentrations of GSK2838232. 3, 6 and 9 month toxicology studies in rat and dog did not demonstrate any evidence of cardiovascular injury or impact on cardiovascular function. In the four GSK2838232 studies conducted so far there was no pattern of cardiovascular changes of clinical significance related to GSK2838232 and no clinically significant abnormality in electrocardiogram values other than the two SAEs documented and discussed. Review of published bevirimat preclinical and clinical safety data indicates no significant toxicities or AEs of interest, other than a 30% incidence of gastrointestinal symptoms (including diarrhea). There were no significant cardiovascular AEs reported in published clinical studies.	Subjects will be clinically monitored for any signs of myocardial injury (chest pain, shortness of breath, pain with inspiration), elevated heart rate or arrhythmias. Samples for the assessment of troponin will be taken. Baseline EKG and Holter (to use for screening and for later comparisons if needed) Exposures of GSK2838232 will be closely monitored in the clinical study so as to not exceed pharmacokinetic stopping criteria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cobicistat (Tybost)		
General	The cobicistat label includes the following information: TYBOST decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating TYBOST In one study investigating cobi+(atazanavir and tenofovir DF/emtricitabine) vs RTV+(atazanavir and tenofovir DF/emtricitabine), a higher frequency of reports of jaundice (6% and 3%) and ocular icterus (4% and 2%) were reported in the cobi group compared to the RTV group. Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides have been observed. The implications of these findings are unknown. The vast majority of available safety data has been obtained in combination studies with other ART. There are no warnings of obvious cobicistat-related adverse events or safety concerns.	Subjects will be closely monitored for any signs or symptoms potentially associated with cobicistat administration, in particularchanges in serum creatinine and liver chemistry.
HIV-1 Infection/Patient population		
HIV Resistance Propensity for co-meds and possible Drug-Drug Interactions (DDIs)	HIV Drug Resistance to unique mechanism Recognize HIV patients have a higher chance of comorbidities/diseases and a risk of taking a medicine or product contraindicated in the study	Closely monitor HIV viral load and genotypic resistance Strict adherence to protocol criteria around concurrent meds

4.4.2. Benefit Assessment

This study in HIV-1 infected but otherwise healthy subjects is a 10-day monotherapy design. It is anticipated that all subjects receiving GSK2838232 will experience anti-HIV effects whereby their (blood) HIV viral titres are reduced, until administration stops and the viral load returns to baseline levels. There is no expected longer term anti-HIV benefit to administration of GSK2838232. Participation in this study contributes to the process of developing GSK2838232 and other new therapies for the treatment of HIV infection.

4.4.3. Overall Benefit:Risk Conclusion

To date, 115 healthy subjects have received GSK2838232 in four completed studies.

Subjects have received single doses up to 200 mg SDD alone (studies HMI116787 and 200912), 250 mg API in combination with RTV (204953), and then in repeated daily doses of up to 50 mg SDD alone (200207) for 5 days or 200 mg in combination with RTV (204953) for 11 days.

There have been two cardiovascular SAEs reported from clinical studies where the subject was receiving GSK2838232 to date (one in 200207, one in 204953). Neither is thought likely to be due to GSK2838232.

There have been no other withdrawals due to drug-related AEs and no trends relative to laboratory toxicity. One subject was withdrawn in Part 1A of 204953 because of low haemoglobin lab values, thought unrelated to study drug or study procedures.

With respect to CV effects, with the exceptions noted, there have been no clinically significant changes in troponin, heart rate, blood pressure, ECG, or telemetry monitoring.

Subjects will also be at risk for AEs from cobicistat use and will be monitored closely for such events.

Given the preclinical profile and the clinical profile to date, the overall risk to HIV-1 infected but otherwise healthy subjects at the proposed GSK2838232 doses (with or without cobicistat) for 10 days is predicted to be low. Mean exposures at the highest dose studied are not projected to exceed NOAEL values obtained in chronic toxicology studies, further reducing potential risk.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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.

Approximately 10-12 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology and PK data analysis, approximately 8 subjects will be enrolled in each of Cohorts 2-4 in Part B. Eligible patients are those who are maturation inhibitor-naïve and who are not currently receiving ART therapy.

Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels or configurations (e.g., GSK2838232 alone).

If subjects prematurely discontinue the study, additional subjects may be enrolled .

5.1. Inclusion Criteria

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

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy (other than HIV infection) male or female as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. Defined as no other chronic medical conditions and taking no chronic medications.
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.
4. A creatinine clearance >80 mL/min as determined by Cockcroft-Gault equation [Cockcroft, 1976] CLcr (mL/min) = (140 – age) * Wt / (72 * Scr) (times 0.85 if female) where age is in years, weight (Wt) is in kg, and serum creatinine (Scr) is in units of mg/dL.
5. Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening.
6. Antiretroviral treatment naive or ART-experienced (maturation inhibitor naive). No current ART (last dose completed at least 6 weeks prior to the first dose of study drug). A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug.

WEIGHT
7. Body weight ≥ 50 kg (110 lbs.) for men and ≥45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-35.0 kg/m^2 (inclusive)

SEX

8. Male or Female
 	
A female subject of reproductive or non-reproductive potential is eligible to participate if she is not pregnant (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test at screening and prior to first dose), not lactating, and at least one of the following conditions applies:
 	
Reproductive potential:
 	
Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. They will be counselled on safer sex practices
 	
There is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.
 	
Fertile females, who have an established, long-term lifestyle of sexual abstinence, or only same sex partners, require no other means of birth control.
 	
Non-reproductive potential:
 	
• Pre-menopausal females with one of the following:
  • Documented tubal ligation
  • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  • Hysterectomy
  • Documented Bilateral Oophorectomy
• Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
 	
Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until one week after the last dose of study medication.
 	
a. Vasectomy with documentation of azoospermia.
 	
b. Male condom plus partner use of one of the contraceptive options below:
  • Contraceptive subdermal implant that meets the SOP effectiveness criteria

including a <1% rate of failure per year, as stated in the product label

- Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
- Oral contraceptive, either combined or progestogen alone or Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

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.

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

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Alanine aminotransferase (ALT) and BIL >1.5xupper limit of normal (ULN; isolated BIL >1.5xULN is acceptable if BIL is fractionated and direct BIL <35%).
2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); HBV and/or HCV positive.
3. Subjects who have any other chronic medical condition, including CV, respiratory, neurologic, psychiatric, renal, gastrointestinal (GI), oncologic, rheumatologic, or dermatologic
4. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.

CONTRAINDICATIONS
5. 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.
RELEVANT HABITS
6. Chronic marijuana or use of other elicit medications (cocaine, heroin) is an exclusion criteria.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
7. Presence of hepatitis B surface antigen (HBsAg), positive (confirmed by Recombinant Immuno-Blot Assay [RIBA]) hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
8. Screening or baseline cardiac troponin I greater than the 99% cutoff (>0.045 ng/mL by the Dimension Vista CTNI assay).
9. A positive pre-study drug/alcohol screen.
10. Prior history of receiving an HIV maturation inhibitor
11. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.
12. 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).
13. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
14. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 30 days of study drug administration or anticipated need for such treatment within the study.
15. Treatment with immunomodulating agents (such as systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (such as hydroxyurea or foscarnet) within 30 days of study drug administration.
16. An active Center for Disease Control and Prevention (CDC) Category C disease except cutaneous Kaposi's sarcoma not requiring systemic therapy during the trial.
17. Treatment with any vaccine within 30 days prior to receiving study medication.
18. Exclusion Criteria for 24-Hour Screening Holter: • Any symptomatic arrhythmia (except isolated extra systoles). • Sustained cardiac arrhythmias (such as atrial fibrillation,flutter or supraventricular tachycardia (≥10 seconds) • Non-sustained or sustained ventricular tachycardia (defined as ≥3 consecutive

ventricular ectopic beats).

- Any conduction abnormality including but not specific to left or complete bundle branch block, atrioventricular [AV] block, high grade or complete heart block Wolff-Parkinson-White [WPW] syndrome etc.).
- Sinus Pauses >3 seconds.

19. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<45 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
*QTc interval	>450 msec	

*The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in 200911 will be Fridericia's formula.

- *Note: A heart rate from 100 to 110 beats per minute (bpm) can be rechecked by ECG or vitals within 30 minutes to verify eligibility.*
- Evidence of previous myocardial infarction (Does not include ST segment changes associated with repolarization).
- Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], WPW syndrome).
- Sinus Pauses >3 seconds.
- Any significant arrhythmia which, in the opinion of the principal investigator OR GSK medical monitor, will interfere with the safety for the individual subject.
- Non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats).

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 any SAEs.

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:

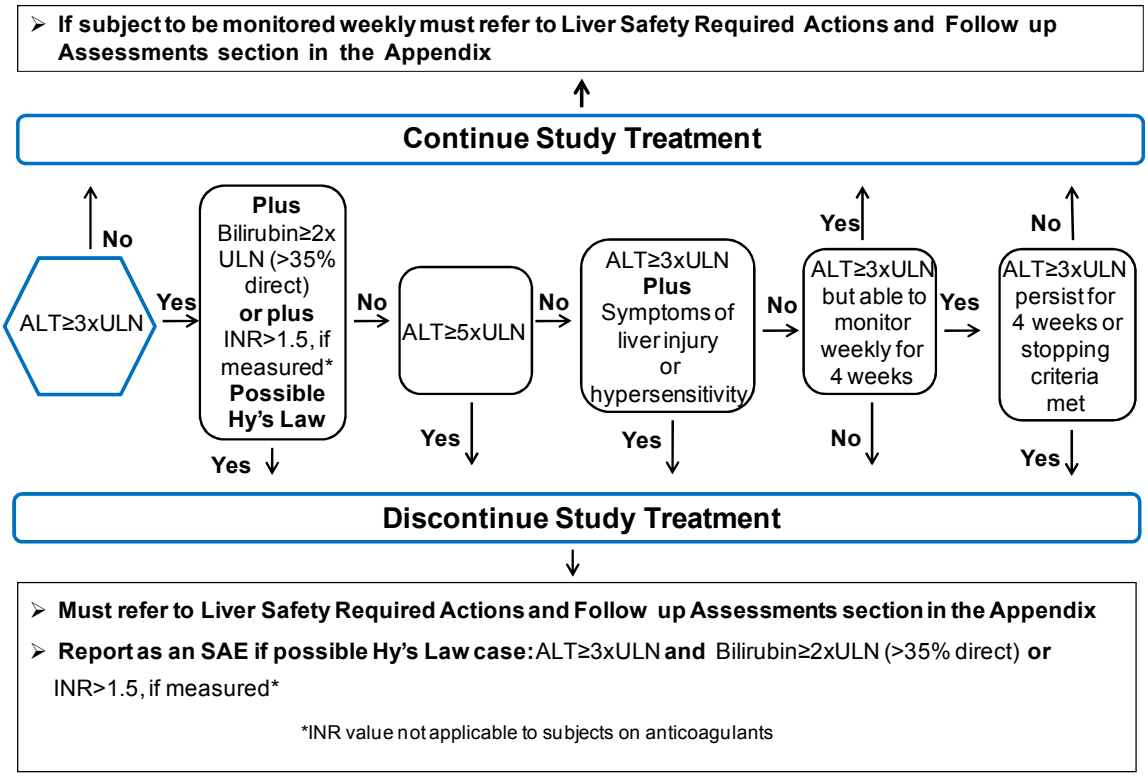
- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where 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 request has occurred in the site study records.

5.4.1. 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).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2, Section 12.2 and Section 12.3.

5.4.1.1. 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.

5.4.2. QTc Stopping Criteria

- The *same* 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.
  - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same 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 ECGs obtained over a brief (e.g., 5-10 minutes) recording period.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

5.5. Stopping criteria based on Adverse Events

Any grade 3 or higher treatment-related adverse events that occur in ≥2 subjects will be carefully reviewed and if considered clinically significant, dosing will be halted pending further discussion with the FDA. Any single treatment-related SAE will also trigger immediate evaluation and reporting processes in accordance with applicable regulations.

5.6. 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.

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Formulation description:	GSK2838232 powder blend in a capsule	Tablet
Dosage form:	Swedish orange, unmarked capsules (50 mg), and white, unmarked capsules (10 mg)	Orange, round, biconvex, film-coated tablets debossed with "GSI" on one side and plain faced on the other side providing 150 mg of cobicistat.
Unit dose strength(s)/ Dosage level(s):	50 mg capsule for 200 mg, 100 mg, 50 mg doses and 10 mg capsule for 20 mg doses	150 mg for 150 mg doses
Route/ Administration/ Duration:	Administered orally QD for 10 days	Administer orally, QD for 10 days

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Dosing instructions:	Administer with light meal and 240 mL of water.	Administer with light meal and 240 mL water.
Manufacturer/ source of procurement:	GSK	Gilead
Method for individualizing dosage:	Capsules supplied in high-density polyethylene bottles for individualized dosing by the clinic	Tablets supplied in bulk containers for individualized dosing by the clinic

6.2. Treatment Assignment

Subjects will be assigned to treatment (active) groups in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

6.3. Planned Dose Adjustments

Following the interim analysis of safety, virology and PK data from the first cohort of subjects in Part A, the option to adjust dose levels from those described exists. No dose will be administered that has an associated projected mean AUC or Cmax value higher than the most conservative NOAEL obtained from the chronic toxicity studies (i.e., from the 9-month dog toxicity study described in Section 2.2.1).

6.4. Blinding

This will be an open-label study. Treatment allocation and GSK2838232 dose levels in Part B will be determined after the analysis of Part A data.

Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for capsule/tablet storage and dispensing will be detailed in a Study Specific Technical Agreement/Memo or Pharmacy Manual, which will be accompanied by a Quality Agreement.

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.
- A Material Safety Data Sheet/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 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.

When subjects self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed through querying the subject during the site visits and documented in the source documents and case report form (CRF). A record of the number of study treatment(s) dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.7. Treatment of Study Treatment Overdose

For this study, any dose of GSK2838232 >200 mg+cobicistat within a 28-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose; however, in the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK2838232 can no longer be detected systemically (at least 10 days for GSK2838232)
- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

- 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 receiving GSK2838232 may opt to receive marketed antiretrovirals after the completion of 10 days of GSK2838232 dosing and study follow-up visits (through Day 21) eligible for sponsor company reimbursement up to a maximum of 90 days. The selection of antiretrovirals will be investigator-chosen.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing reimbursement for post-study treatment.

6.9. Lifestyle and/or Dietary Restrictions

6.9.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice from 7 days prior to the first dose of study medication until after the final dose.
- Doses will be given in the fed state (light breakfast), following overnight fasting (>10 hours).

6.9.2. Alcohol, Caffeine and Exercise

- During the study alcohol consumption should be limited to the following:
    - An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.
- Subjects should abstain from strenuous exercise during the treatment period.

6.10. Contraception

Female subjects can be of childbearing or non-child bearing potential.

Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. Although use of oral contraceptives is permitted, there is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.

Females of reproductive potential, who have an established, long-term lifestyle of sexual abstinence, or only same sex partners, require no other means of birth control.

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until one week after the last dose of study medication:

1. Vasectomy with documentation of azoospermia. 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.

OR

2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

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.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

- Acetaminophen at doses of ≤2 grams/day or NSAIDs are permitted for use any time during the study and their use documented in the CRF. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required.
- Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Subjects must notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications.

6.11.2. Prohibited Medications and Non-Drug Therapies

- Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 and at additional timepoints throughout the study. A positive result will lead to exclusion from the remainder of the study.

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 (Section 7.1), 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. In overview, subjects will be screened, begin dosing and then continue assessments through and for up to 2 weeks after the completion of dosing.

The following points must be noted:

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

    1. 12-lead ECG
    2. vital signs
    3. blood draws.

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

7.1. Time and Events Table

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Informed Consent	X																
Review inclusion/exclusion	X		X														
Demography including height, weight and BMI	X																
Brief physical			X														
Medical/medication/ drug/alcohol history	X		X														
CDC Classification	X		X													X	X
Prior antiretroviral therapy	X																
12-lead ECG[3]	X		X			X				X		X	X	X		X	X
Holter (24 hr)	X																
Vital signs[4]	X		X			X	X			X		X		X		X	X
Drug screen	X		X			X						X				X	
Hepatitis B Surface antigen and hepatitis C antibody testing	X																
Serum or urine β-hCG (WoCBP only)	X		X														X
Clinical lab tests (inc troponin)	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Fasting lipid panel	X																X
AE assessment[5]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Con Medication Review	X		X	X	X	X	X			X	X	X	X	X	X	X	X
HIV-1 RNA PCR[6]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Lymphocyte subsets[7]	X		X										X				
Plasma for genotype/phenotype[8]			X			X	X			X			X			X	X
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		X[14]
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Telephone call to IVRS[13]	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X
Plasma for storage[15]			X	X	X	X	X			X	X	X	X	X	X	X	X
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

1. Screening will occur within 14 - 30 days prior to the first dose of study drug.
2. Table is set up for the weekend during dosing to occur on Days 6 and 7. If the weekend occurs on Days 5 and 6, perform all "Day 5" assessments on Day 7.
3. On Day 1, ECGs will be performed pre-dose , and then 1, 1.5, 2, 3, 4 and 6 hours post dose. The ECGs should be performed at least 5 minutes apart and preferably within 1 hour prior to dose. On Days 4 and 8, ECGs will be obtained prior to morning dosing and at 2, 4 and 6 hours post-dose. To accommodate scheduling, serial ECGs collected on Days 4 and 8 may be performed ± 1 day. On Day 10, ECGs will be performed pre-dose, and then 1, 1.5, 2, 3, 4 and 6 hours post dose. On Day 11, an ECG will be obtained prior to the 24-hour PK sample. ECGs will be performed in triplicate at all timepoints.
4. BP, RR, HR and temperature will be obtained at Screening (x1) and Day 1 pre-dose (x2). BP and HR will be obtained on Day 1 at 2 hours post-morning dose and on Days 4, 5 and 8 pre-dose. BP and HR will be obtained on Day 10 at pre-dose and 2 hours post-morning dose, and at day 12 and Follow-up (Day 21).
5. Only SAEs related to study participation will be collected between screening and Day 1. An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status.
6. On Days 1-5 and 8-10 samples for HIV-1 RNA PCR collected before morning dose. On Days 1, 10 and 11 two samples for HIV-1 RNA PCR will be collected 5-30 minutes apart. HIV-1 RNA PCR samples will also be collected on days 12, 14 & Follow-up (Day 21).
7. Lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+and CD8+counts).
8. Blood samples for phenotype and genotype will be collected at pre-dose on Days 1, 4, 5 and 8 in the morning on Day 11 and at follow-up.
9. Serial plasma samples (2 mL) for determination of GSK2838232 will be collected on Day 1 and Day 10 at pre dose (within 15 minutes prior to dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 (optional), and 24 hours (to occur on morning of Day 2 post-am dose and in the morning on Day 11) . Pre-dose PK samples (within 15 minutes prior to dose) will be taken on the mornings of Days 3, 4, 5, 8 and 9 and a single sample will be taken on Days 12 and 14.
10. Samples (2 x 0.5mL) of plasma for assessment of immunological markers at screen, baseline (pre-dose) and day 11
11. Subjects will receive a single dose of GSK2838232 and cobicistat each morning with a light breakfast meal and 240 mL of water from Day 1 to Day 10. Doses taken in the clinic will be administered after an overnight fast of at least 10 hours .On Days 6 and 7, doses will be self administered but confirmed by phone
12. PGx sample should be collected on Day 1.
13. A screening/registration call should be made to the IVRS to register the subject at screening. An additional call will be made to document a screen failure. A randomization call should be made to the IVRS system approximately one week prior to scheduled Day 1. Note: The randomization call must be made in order to have study drug on site for Day 1. Additional calls will be made every day that the subject has a scheduled study visit to the clinic. If a subject terminates the study prematurely a call should be made to the IVRS
14. Only if early termination visits occur during the treatment period.
15. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally these samples will be used when needed, such as when samples are lost or arrive at the laboratory unevaluable.

AE = Adverse event; CDC= Center for Disease Control and Prevention; ECG = Electrocardiogram; ET = Early termination; hCG = Human chorionic gonadotrophin; HIV = Human immunodeficiency virus; IVRS= Interactive Voice Response System; PCR = Polymerase chain reaction; PK=Pharmacokinetic.

7.2. Visit Windows

Screening (baseline to pre-dose): All screening assessments should take place within 14-21 days prior to the first dose. The screening visit window may be extended to 30 days upon discussion with the Medical Monitor (i.e.; subject has scheduling conflicts or any screening assessment needs to be repeated).

Days 4 and 8: Based on subject and clinic schedule, Day 4 and Day 8 serial (up to 6h post-dose) ECG assessments may be conducted ± 1 day.

Weekend(s): The T&E table is set up for study start (Day 1) to occur on a Monday and Days 6 and 7 to fall on the weekend. If the weekend occurs instead on Days 5 and 6, Day 5 assessments should be performed on Day 7. The study start (Day 1) may also be adjusted to allow visits with assessments to be conducted over the weekend based on subject and clinic schedule.

Assessments: The following applies to timing of procedures:

- Window for assessments ≤ 4 h post-dose = ± 5 minutes
- Window for assessments >4 and < 12 h post-dose = ± 15 minutes
- Window for assessments >12 h post-dose = ± 30 minutes

End of Treatment visit: should be within 14 days from last dose of study drug. If a subject is unable to return to the clinic for any reason site staff are encouraged to telephone the subject for assessment of adverse events.

7.3. 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.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.3.1. Holter Monitoring (Screening criteria)

The 24-hour Holter monitoring will be performed during the Screening period using a Holter monitoring device supplied by the Sponsor.

Analysis of the Holter tapes will consider the following:

- Heart rate (bradycardia and tachycardia)
- Normal and aberrant beats
- Number of supraventricular contractions, premature atrial contractions, premature ventricular contractions, couplets, triplets, and ventricular tachycardias
- Atrio-ventricular conduction defects
- Atrial fibrillation and flutter

7.4. Efficacy

7.4.1. HIV-1 RNA Sampling

Plasma for quantitative HIV-1 RNA will be collected at timepoints listed in the Time and Events Table in Section 7.1. To reduce sample variability, two plasma HIV-1 RNA samples will be collected on Days 1, 10, and 11.

An HIV-1 RNA PCR assay with a lower limit of detection (LLOD) of 50 copies/mL (ultrasensitive assay) will be used for post-baseline assessments. An HIV-1 RNA PCR assay with a LLOD of 400 copies/mL (standard assay) will be used for screening and baseline assessments and will include a re-test with and ultrasensitive assay for all baseline values below the LLOD. An HIV-1 RNA PCR assay with a LLOD of 2 copies/mL (supersensitive assay) may be used for exploratory analysis.

7.4.2. Lymphocyte Subsets by Flow Cytometry

Whole venous blood samples will be obtained from each subject for the analysis of lymphocyte subsets by flow cytometry at the timepoints listed in the Time and Events Table in Section 7.1.

Details concerning the handling, labeling and shipping of these samples will be supplied separately.

7.5. 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.

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

The definitions of an AE or SAE can be found in Appendix 5, Section 12.5.

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

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.5.1.3), at the timepoints specified in the Time and Events Table (Section 7.1). An AE enquiry will be made at each visit, where subjects will be specifically asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to Sponsor within 24 hours, as indicated in Appendix 5, Section 12.5.
- 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 5

7.5.1.2. 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?”
- “Have you experienced any alteration in personality, behaviour, mood or any altered mental status?”

7.5.1.3. 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, and non-serious AEs of special interest (as defined in Section 12.5) 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 5.

7.5.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 (Section 12.5.3) and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

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

The following disease-related events (DREs) are common in subjects with HIV-1 infection and can be serious/life threatening:

- events or outcomes listed in the CDC Classification System for HIV-1 Infections (see Appendix 9; Section 12.8)
- sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a serious adverse event).

These events will be recorded on the DRE page in the subject's CRF using the HIV Associated Conditions eCRF. These DREs will be monitored by the medical monitor and study team on routine basis.

However, if any of the following conditions apply, then the event should be reported as an SAE using the standard process:

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject,
  or
- The Investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.
  or

- Death occurring for any reason during a study, including death due to a disease related event, will always be reported promptly.

If either of the above conditions is met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly to GSK.

7.5.1.6. Regulatory Reporting Requirements for SAE

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs 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.

7.5.2. Pregnancy

- Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until one week post study
- If a pregnancy is reported then the investigator should inform GSK within 24hrs of learning of the pregnancy and should follow the procedures outlined in Appendix 7, Section 12.6.

7.5.3. Physical Exams

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

7.5.4. Vital Signs

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

7.5.5. Electrocardiogram (EGC)

- Triplicate 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.5.6. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments as defined in the Tables below must be conducted in accordance with the SRM and Protocol Time and Events Schedule (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled 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 SRM. 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 SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory:

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered in the CRF.

Haematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed below.

Table 9 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes with T-cell subsets	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Bicarbonates	Alkaline phosphatise	Albumin
	Troponin I			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]			

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 12.2 and Section 12.3
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 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.

7.6. Pharmacokinetics

7.6.1. Blood Sample Collection

Blood samples for analysis of GSK2838232 concentrations will be collected at the time points indicated in Time and Events Tables (Section 7.1).

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.6.2. Sample Analysis

Plasma analysis will be performed by Covance, Madison under the control of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS, GlaxoSmithKline. Concentrations of GSK2838232 will be determined in plasma using the currently approved bioanalytical methodology.

Once the plasma has been analyzed for GSK2838232 any remaining plasma may be analyzed qualitatively for other circulating metabolites and these results would be reported under a separate PTS protocol.

Raw data will be archived at the Covance, Madison facility.

7.7. Biomarker(s)/Pharmacodynamic Markers

7.7.1. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide plasma for viral genotype and phenotype analysis, at the times listed in the Time and Events Table in Section 7.1. Details concerning the handling, labeling and shipping of these samples will be supplied separately.

Genotypic and phenotypic analyses will be carried out by Monogram Biosciences using their GAG/PR and PR/RT formats, in which PCR amplification is used to generate HIV cDNA products including the Gag and the PR and RT coding regions, respectively. Phenotypic analyses of the GAG/PR region will include susceptibility to GSK2838232 . Analysis will be done on Day 1 and Day 11 samples. In the case of rebound HIV-1 viral load, analysis will be completed on samples corresponding to time point of rebound occurrence.

7.8. Genetics

Information regarding genetic research is included in Appendix 4, Section 12.4.

7.9. Value Evidence and Outcomes

Not required.

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 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

The primary objectives of this study are to investigate the safety, tolerability, and antiviral activity of GSK2838232 administered as monotherapy in combination with cobicistat in HIV-1 infected subjects, over a 10 day treatment period. The antiviral activity will be assessed by estimating plasma HIV-1 RNA max change from baseline during the study.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size for this study is based primarily on feasibility to provide adequate precision for the estimations.

Based on data from the short term monotherapy study of BMS-955176 PoC (AI468002) study and assuming viral load values for individual subjects follow a log-normal distribution, 1000 trial simulations in Fixed and Adaptive Clinical Trial Simulation (*FACTS*) software were conducted from the distribution with mean of change from baseline viral load drop on log scale at 1.0 to 1.5 copies and SD=0.4 and sample sizes=10 for Part A. Using Bayesian calculation with non-informative priors for the mean and weakly informative priors for the error parameters, Normal (0, 100) for mean and Inverse Gamma (0.35, 0.0875) for error parameters, the posterior probability to achieve a cutpoint 1.2 log was calculated for each simulated trial, and percentage of the trials with

posterior probability of viral load<-1.2log drop given true mean) ≥70% were calculated and are shown below in Table 10.

Table 10 Percentage of the trials with posterior probability>=70% for Part A

True Mean	Cutpoint	Posterior Prob>=70%
1.0	1.2	1.4%
1.1	1.2	9%
1.2	1.2	29%
1.3	1.2	59%
1.4	1.2	83%
1.5	1.2	96%

An Emax model with functional uniform priors [Bornkamp, 2014] was conducted using simulated data combining Part A and Part B with all doses. Success is defined as a posterior probability of the highest dose to achieve a cutpoint 1.2 log reduction in viral load. This was calculated for each simulated trial and the percentage of the trials with posterior probability greater or equal to 70% were also calculated and are shown below (Table 11). The table lists different viral load drop scenarios. The last scenario assumes the flat drop for all doses are 0.5. This scenario reflects the null hypothesis of no treatment effect. In this scenario 0% of the trials achieve the pre-specified decision rule for success.

Table 11 Percentage of the trials with posterior probability ≥70%

Cutpoint	Posterior Prob≥	Part A+ Part B mean VL drop for doses 200, 100, 50, 20	Part A+ Part B
1.2	70%	1.5, 1.4, 1.2, 0	99%
		1.5, 1.4, 1.2, 0.5	96%
		1.5, 1.4, 1.0, 0.5	93%
		1.5, 1.3, 1.2, 0.5	86%
		0.5, 0.5, 0.5, 0.5	0%

9.2.2. Sample Size Sensitivity

Similar simulations in FACTS were conducted from the distribution with mean of change from baseline viral load drop on log scale at 1.5 copies and SD=0.4 or 0.6 and sample sizes of 6-8 or 10 for Part A. Using Bayesian calculation, the posterior probability to achieve a cutpoint 1.2 log (in Table 12) was calculated for each simulated trial, and percentage of the trials with posterior probability greater than or equal to 70% was calculated and are shown below.

Table 12 Percentage of the trials with posterior probability ≥70% for Part A

True Mean	Cutpoint	Posterior Prob≥	Std for log10 VL	N=6	N=8	N=10
1.5	1.2	70%	0.4	90%	94%	96%
			0.6	75%	81%	84%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Intent to Treat Exposed Population (ITT)

The ITT-Exposed Population is defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received at least 1 dose of treatment and at least one post-baseline HIV-1 RNA measurement. This will be the primary population for the final efficacy analysis for all active treatment groups.

Per Protocol Population (PP)

The Per Protocol Population is defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received all doses and all post-baseline HIV-1 RNA measurement, with exceptions of major protocol deviation.

Safety Population

The Safety Population is defined as all subjects who are enrolled into the study with documented evidence of having received at least 1 dose of randomized treatment.

Pharmacokinetic Population

The PK Population will include all subjects who receive GSK2838232 and undergo plasma PK sampling during the study. Subjects for whom a plasma PK sample is obtained and assayed will be included in the listing of plasma GSK2838232 concentration-time data. Results from samples collected from a subject with emesis occurring within 4 hours of the dose will not be considered as evaluable.

9.3.2. Interim Analysis

An interim analysis of preliminary safety, tolerability, PK and antiviral activity will occur after subjects of Part A Cohort 1 complete their Day 13 visit. If the Cohort 1 dose is determined to be the highest dose based on this review (e.g., the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects), the Bayesian posterior probability that the log10 viral load decline from baseline is greater than a cut-point will be calculated. If the Bayesian probability from Cohort 1 is less than 70%, this will provide evidence to not move forward into Part B. Otherwise, the study team will review the data in order to make a dose selection decision for the subsequent Part B Cohorts. If the pharmacokinetic exposures after the 100 mg GSK2838232/cobi dose look similar to those obtained with 100 mg GSK2838232/r in

prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) GSK2838232 doses.

Maximum change and change from baseline in plasma HIV-1 RNA will be summarized by treatment or by assessment day. The proportion of subjects with plasma HIV-1 RNA <400 and <50 copies/mL will be summarized by treatment and assessment day. The analyses will be done for both PP and ITT exposed population if the two populations are not the same.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The 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 will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and %CVb for continuous variables, 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 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings. Complete details will be documented in the Reporting and Analysis Plan (RAP).

9.4.1.1. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library standards and data will be in CDISC format. No formal statistical analysis of the safety data will be conducted.

9.4.1.2. Efficacy Analyses

Both the PP and ITT Populations will be used for all efficacy analyses if there are dropouts. Plasma HIV-1 RNA max change and change from baseline during the study will be calculated for each subject on each assessment day.

Plasma HIV-1 RNA will be listed by treatment, subject, and assessment day and summarized by treatment and assessment day along with change from baseline.

Plots of mean and median plasma HIV-1 RNA actual and change from baseline data will be generated by treatment and assessment day.

- Plasma HIV-1 RNA change from baseline to the on-treatment nadir (maximum change) will be calculated for each subject and summarized by treatment.

Together, the data from Parts A and B will investigate the complete dose-response curve and the impact of lower doses on potential development of resistance. A dose-response curve will be fit to the data from Parts A & B using functional uniform priors.

9.4.1.3. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling and Simulation Department, GlaxoSmithKline. Plasma GSK2838232 concentration-time data will be analyzed by non-compartmental methods with WinNonlin Version 6.1 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:

Plasma GSK2838232 Pharmacokinetic Parameters to be Estimated:

Study Day	Parameters
1	AUC(0-24), Cmax, tmax, tlag, C24
10	AUC(0-τ), Cmax, tmax, t½, C0, Cτ, CL/F, R_AUC, R_Cmax, R_Cτ

Results based on samples collected from a subject with emesis within 4 hours of the dose will not be considered as evaluable.

All PK data will be stored in the R&D archives, GlaxoSmithKline.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline. Details of the statistical analyses will be provided in the RAP. An outline is provided below:

Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. Plasma GSK2838232 PK parameters, with the exception of tmax and tlag, will be log-transformed prior to analysis.

Dose proportionality of plasma GSK2838232 PK parameters from Day 1 [AUC(0-24) and Cmax] and Day 10 [AUC(0-τ) and Cmax] will be assessed using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI. The accumulation ratio (R) and steady-state assessments will be performed, if quality of the data permits. Comparisons of Day 10 with Day 1 PK for each dose will be used for the accumulation ratio (R) evaluation. Pre-dose concentrations between Days 7-10 will be used for steady-state assessment.

9.4.2. Secondary Analyses

9.4.2.1. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between various PK parameters (e.g., AUC, Cmax, Cτ, etc.) and PD measures (e.g., log10 reduction from baseline in plasma HIV-1 RNA on Day 11 or safety

parameters) will be explored using various models including Emax. The relationship between dose and PD measures will also be explored. Details of the PK/PD exploratory analyses will be provided in the RAP.

9.4.2.2. Viral Genotyping and Phenotyping Analyses

Viral genotypic/phenotypic data will be listed and descriptive summaries will be provided. Details of the analyses will be provided in the clinical virology report.

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 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 or designee 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 or designee 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.

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.

10.8. Review Committees

The Safety Review Team (SRT) is a GSK cross-functional team reviewing all available safety data related to the project, including in-stream data from this study, in an ongoing manner. The SRT is an internal GSK requirement put in place to ensure holistic evaluation of the safety profile of an investigational product with systematic, periodic and documented reviews of available safety data, with the appropriate communication and escalation of new findings that have the potential to impact patient safety

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

µg/mL	Microgram per millilitre
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredient
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUC(0-24)	Area under the concentration-time curve from zero (pre-dose) to 24 h
AUC(0-48)	Area under the concentration-time curve from zero (pre-dose) to 48 h
AUC(0-t)	Area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration
BCRP	Breast cancer resistance protein
BID	Twice daily
Bpm	beats per minute
BVM	Bevirimat
BIL	Bilirubin
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
C24	24 hour trough concentration
CDC	Center for Disease Control and Prevention
CI	Confidence interval
CL/F	Oral Clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CPK	Creatine Phosphokinase
CRF	Case report form
cTnI	Cardiac troponin I
CV	Coefficient of variation
CVb	Between-subject variability
CYP	Cytochrome P450
DDI	Drug Drug Interaction
DNA	Deoxyribonucleic acid
EC50	50% protection against resistant mutant HIV infection

ECG	Electrocardiogram
FC	Fold Changes
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FTIH	First time in Human Study
g	Gram
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour(s)
HBsAg	Hepatitis B surface antigen
hcG	Human chorionic gonadotrophin
HDPE	High density polyethylene
hERG	Human Ether-a-gogo Related Gene
HIV	Human Immunodeficiency Virus
IC50/90	50% or 90% maximal inhibitory concentration
IEC	International Ethics Committee
IQ	Inhibitory quotient
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous
IVRS	Interactive voice response system
kg	Kilogram
L	Litre
LLOD	Lower limit of detection
MC	Melanocortin
MedDRA	Medical Dictionary for Regulatory Activities
mg/mL	Milligram per millilitre
MI	Maturation inhibitor
mL	Milliliter
mRNA	messenger Ribonucleic Acid
ND	Not done
ng/mL	Nanogram per millilitre
nm	Nanometer
NO	Not observed
NOAEL	No Observed Adverse Effect Level
NTproBNP	N-terminal prohormone of brain natriuretic peptide
NSVT	Non-sustained ventricular tachycardia
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBL	Peripheral Blood Lymphocytes
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamics
PPD	Pharmaceutical Product Development
P-gp	P-glycoprotein
PHIV	Pseudo- HIV

PiB	Powder-in-bottle
PK	Pharmacokinetic
PoC	Proof of Concept
PI	Protease Inhibitor
QD	Once daily
RAP	Reporting and analysis plan
RIBA	Recombinant Immuno-Blot Assay
RT	Reverse Transcriptase
SAE	Serious adverse event
SDD	Spray Dried Dispersion
SRM	Study reference manual
t½	Terminal elimination half-life
TEM	Transmission Electron Microscopy
tlag	Time of first quantifiable concentration
tmax	Time of occurrence of Cmax
U	Units
UGT	Uridine 5'-diphospho-glucuronosyltransferase
Vz/F	Mean apparent oral volume of distribution
WPW	Wolff-Parkinson-White

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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Chiron RIBA
Inform
Monogram
Phoenix WinNonlin
SAS
Tybost (cobicistat)

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

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

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin1, 2</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR2</td><td colspan="2">ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic3</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted
• If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and may continue subject in the study</td><td colspan="2">• Viral hepatitis serology[4]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 24hrs after last dose[5]
• 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</td></tr>
</table>

for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high-performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week • 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. 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.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

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

12.4. Appendix 4: Genetic Research

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK2838232/RTV 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 or 2 ml saliva sample will be taken for Deoxyribonucleic acid (DNA) extraction. A 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/saliva 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/saliva 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/saliva 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.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT 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.

12.5.2. 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:
c. Results in death
d. 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.
e. 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.

f. 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

g. Is a congenital anomaly/birth defect

h. 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

i. 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.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Definition of Cardiovascular Events

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

12.5.4. 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. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by

the scale's developer.

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.5.5. 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.

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.
- By specific request, the investigator is obligated to report any grade 2 or higher "alteration in personality-behavior or in mood" or "altered mental status" adverse events that occur in subjects taking this drug, to GSK within 3 days.
- 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.

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data

on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.

- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF

- Facsim0ile 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.

SAE reporting to GSK via PIMS

- Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the Medical Monitor or protocol contact:
  - SAE listing
  - Demographic listing
  - Study treatment listing
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
- If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the Medical Monitor or protocol contact. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.6. Appendix 6: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24hrs 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 discontinue study medication and be withdrawn from the study
- This will only be included if either of the following apply:
- 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 report the event and submit it to GSK within 24hrs 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.

12.7. Appendix 7: Country Specific Requirements

No country-specific requirements exist.

12.8. Appendix 8: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events Version 1.0, December 2004; Clarification August 2009

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
DERMATOLOGIC				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE AND METABOLIC				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia **Report only one and specify location**	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< *30 years of age*	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] ≥ *30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< *30 years of age*	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
NEUROLOGIC				
Acute Central nervous system (CNS) Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay < *18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures *New Onset Seizure* ≥ *18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< *18 years of age* *(includes new or pre-existing febrile seizures)*	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
PREGNANCY, PUERPERIUM, AND PERINATAL				
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	World Health Organization (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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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 < Lower limit of normal (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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 Estimated glomerular filtration rate (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*
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Low Density Lipoprotein (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*
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY				
Absolute cluster of differentiation 4 (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

1. Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
2. As per Bazett's formula.
3. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
4. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.
6. Bone mineral density (BMD) t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.
7. Definition: A delivery of a live-born neonate occurring at ≥20 to <37 weeks gestational age.
8. Definition: A clinically recognized pregnancy occurring at <20 weeks gestational age.
9. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
11. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12. WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.
13. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
14. Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as Grade 2, if <10% of the total bilirubin.
15. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
16. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
17. Male and female sexes are defined as sex at birth.
18. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

12.9. Appendix 9: 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:

20. peripheral blood smear
21. indirect bilirubin (abnormal if increased >50% from baseline)
22. haptoglobin (abnormal if ≤ 25 mg/dL)
23. 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:

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. 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:

5. peripheral blood smear
6. indirect bilirubin
7. haptoglobin
8. 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 9.

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:

9. Temperature > 38.5°C
10. Lymphadenopathy
11. Pharyngitis
12. 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 10.5.

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:

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 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 10.5.

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 10.5.

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 24 hours via phone or fax. The subject should be closely followed everyday until resolution of the reaction. The subject should remain on the study to be followed for safety and PK as outlined in Section 10.5.

ALLERGIC REACTION

Grade 1 allergic reaction (Pruritis 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:

17. Temperature > 38.5°C
18. Eosinophilia
19. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
20. 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.

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:

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 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.

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

12.10. Appendix 10: Protocol Amendment Changes

12.10.1. AMENDMENT 1

Protocol Amendment 1 (26-Apr-2017) from the original protocol (09-Nov-2016)

Where the Amendment Applies

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

List of Specific Changes: (**bold** indicates text added and ~~strikethrough~~ indicates text removed)

Summary of Protocol Amendment Changes with Rationale

Amendment 1 includes minor updates to Inclusion criteria (IE) criteria, including clarification on use of pre- or post-exposure prophylaxis, and removal of exclusionary requirements related to concomitant medications and tobacco and alcohol use during the study. Guidance around relevant habits is included in the Lifestyle section of the protocol and adjustments were made to reduce restrictions on these requirements. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirements. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Furthermore, the serial ECG collection (up to 6h post-dose) was removed on Day 5. Finally, the post-study care guidance was updated to include an option for subjects to receive reimbursement for marketed ART for a limited period after completion of study treatment and follow up. Minor clarifications, reformatting of tables, re-numbering of sections and correction of typographical errors were also made throughout this amendment.

List of Authors

Rationale for change

The list of authors was updated based on internal GSK team personnel changes.

Revised Text

PPD

PTS, Ware, UK

GCSP, Stockley Park, UK

Infectious Diseases, Clinical, Upper Providence, PA, US

Clinical Statistics, GSK, Upper Providence, PA, US

HIV DPU, RTP, NC, US

Virology, HIV DPU, RTP, NC, US

PPD

CPMS, GSK, RTP, NC, US

HIV DPU, RTP, NC, US

Clinical Pharmacology, ViiV Healthcare, RTP, NC, US

PCPS, GSK, Upper Providence, PA, US

PCPS, GSK, Collegeville, PA, US

~~Clinical Statistics, PAREXEL, RTP, NC, US~~

~~Infectious Diseases, Clinical, Cambridge, MA, US~~

Medical Monitor/SAE Contact Information

Rationale for change

The sponsor and medical monitoring information was updated to reflect the current contact information for safety and medical monitoring.

Revised Text

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor/**SAE contact information**	PPD ~~MD~~ **Pharmaceutical Product Development (PPD) Safety Hotline**	PPD			~~Boston, MA~~**PPD, 929 North Front Street, Wilmington, NC 28401**
Secondary Medical Monitor	PPD MD				GlaxoSmithKline 1250 St Collegeville Rd Collegeville, PA 19426
~~SAE contact information~~	PPD ~~MD~~				~~Boston, MA~~

Synopsis: Design, Treatment Arms and Duration

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced. As synopsis being a standalone document, cross-referenced has been removed.

Revised Text

Fourth paragraph

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from ~~ongoing~~ Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) ~~is being~~ **was** assessed.

Sixth paragraph

HIV Drug Resistance: Following cessation of GSK2838232/cobi dosing for 10 days, there will be prolonged exposure to waning plasma concentrations of GSK2838232, because of the long t½ (i.e., in the "tail" of the PK profile). However, based on in vitro resistance passage data with GSK2838232 [and unlike with many other ARV therapies], there appears to be a limited likelihood of developing maturation resistance mutations in HIV-infected subjects due to its virologic ~~profile [GSK Document Number 2013N163221_00]~~.

Section 2 Introduction

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

GSK2838232 is a novel **human immunodeficiency virus (**HIV**)**-1 maturation inhibitor (MI) that is being developed for the treatment of HIV-1 infection in combination with other antiretrovirals (ART).

Section 2.1 Study Rationale

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

This 'proof of concept (PoC)' open-label study is being conducted to characterize the acute antiviral activity, pharmacokinetics (PK), the relationship between PK and antiviral activity, and safety of GSK2838232 given with 150 mg **once daily (**QD**)** cobicistat (GSK283232/cobi), administered across a range of doses over 10 days in HIV-1 infected patients. A two part adaptive and dose ranging design is to be applied in this study. Data from this study will be utilized to select doses for further studies in Phase IIb.

Section 2.2 Brief Background

Rationale for change

Abbreviation used on first instance has been defined.

Addition of abbreviation for AIDS in first paragraph

Combination antiviral therapy with inhibitors of HIV protease, integrase, entry and reverse transcriptase (RT) has demonstrated significant improvement in **acquired immunodeficiency syndrome** (AIDS)-related morbidity and mortality over the last 10-15 years.

Addition of abbreviation for RNA in second paragraph

Prior validation of this target was demonstrated with the HIV maturation inhibitor known as bevirimat (BVM; [Martin, 2007a; Martin, 2007b; Martin, 2008; NORVIR, 2013]). BVM reached Phase II studies in HIV patients; however, only modest reductions in plasma HIV-1 ribonucleic acid (RNA) concentrations were observed in Phase IIa monotherapy studies [Mahmood, 2006; Martin, 2007] and a pattern of polymorphic (differential) antiviral activity [Wainburg, 2010] led to termination of BVM development. The average decrease from baseline to Day 14 plasma HIV-1 **ribonucleic acid** (RNA) was 0.54 and 0.70 log10 copies/mL for 200 mg and 300 mg twice daily regimens (Table 2); all subjects achieved plasma BVM concentrations above the in vitro EC90. Responders, classified based on 5 polymorphisms in HIV-1 gag (at positions 369, 370, and 371), achieved an average 1.15 log10 copies/mL reduction in plasma HIV-1 RNA, while an average 0.17 log10 copies/mL reduction was achieved for non-responders.

Section 2.2.2 Clinical Summary of Safety and Pharmacokinetics

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Revised Text

To date, GSK2838232 has been evaluated in three completed clinical studies with or without **ritonavir** (RTV) (GSK2838232/r). A fourth study (204953) ~~is on-going as of 1st November~~ **completed late** 2016 **and data analysis is ongoing**. Full details of the clinical results can be found in the Investigator's Brochure.

Section 2.2.2.1 Clinical Summary of Safety

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Revised Text

~~Fifty~~ **As of November 2016 fifty**-three subjects ~~have~~ **had** been exposed to GSK2838232 in 3 completed studies. One study (204953) ~~is~~ **completed in late 2016 and the analysis of results are** ongoing (~~52 subjects have been~~ **63 subjects were** exposed to GSK2838232/r or placebo so far **in this study**). Overall, drug-related adverse events have been few and mild, and included headache, dizziness, fatigue, nausea, and palpitations and anxiety. Similarly, treatment-emergent laboratory abnormalities have also been few and mostly grade 1. There have been no discernible patterns, thus far, in terms of AEs or laboratory abnormalities.

Section 2.2.2.2 Study 204953 (completed); Pharmacokinetic Data

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Change in Heading

Section 2.2.2.2 Study 204953 (~~on-going~~ **completed**); Pharmacokinetic Data

Section 4.4.1 Risk Assessment

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
HIV-1 Infection/Patient population		
HIV Resistance Propensity for co-meds and possible **Drug-Drug Interactions (**DDIs**)**	HIV Drug Resistance to unique mechanism Recognize HIV patients have a higher chance of comorbidities/diseases and a risk of taking a medicine or product contraindicated in the study	Closely monitor HIV viral load and genotypic resistance Strict adherence to protocol criteria around concurrent meds

Section 5.1 Inclusion Criteria

Rationale for change

Changes were made to this inclusion criteria to clarify that prior use of pre- or post-exposure prophylaxis would not exclude a subject from participation as long as last dose was 6 weeks before starting study treatment.

Revised Text

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY

5 . Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening. No current and no prior ART. **(A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug).**

Section 5.2 Exclusion Criteria

Rationale for change

This exclusion criteria was removed and the guidance for use of concomitant medications was further addressed in Section 6.12, Concomitant Medications and Non-Drug Therapies. The Relevant Habits section of the Exclusionary criteria was also removed and addressed in Section 6.10, Lifestyle and/or Dietary Restrictions, with the exception of illicit drug use. Smoking and limited alcohol use are no longer exclusionary. Additional clarification added to note that positive Hepatitis C result would need to be confirmed by RIBA. Abbreviation used on first instance has been defined. Additional minor typographical errors were corrected.

Revised Text

~~CONCOMITANT MEDICATIONS~~
~~5. 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 GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.~~

RELEVANT HABITS
~~6. History of regular alcohol consumption within 6 months of the study defined as:~~ ~~• An average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.~~ ~~7. Smoking is an exclusion criteria for this study. Urinary cotinine levels indicative of~~

~~smoking at screening.~~

6. Chronic marijuana or use of other elicit medications (cocaine, heroin) is an exclusion criteria.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

7 . Presence of hepatitis B surface antigen (HBsAg), positive **(confirmed by Recombinant Immuno-Blot Assay [RIBA])** hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.

19 . Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<45 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
*QTc interval	>450 msec	

*The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in ~~204953~~**200911** will be Fridericia's formula.

Section 6.1 Investigational Product and Other Study Treatment

Rationale for change

Minor typographical error corrected in this section.

Revised Text

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Method for individualizing dosage:	Capsules supplied in high-density polyethylene bottles for individualized dosing by the clinic	~~Capsules~~ **Tablets** supplied in bulk containers for individualized dosing by the clinic

Section 6.9 Treatment after the End of the Study

Rationale for change

Additional language was included in this section to allow subjects to opt to receive reimbursement from GSK for up to 3 months for marketed antiretroviral therapy (as

directed and prescribed by physician) based on the CDC guideline recommendations that patients be put on ARTs when diagnosed with HIV (test and treat guidelines).

Revised Text

~~Subjects will not receive any additional treatment from GSK.~~

Subjects receiving GSK2838232 may opt to receive marketed antiretrovirals after the completion of 10 days of GSK2838232 dosing and study follow-up visits (through Day 21) eligible for sponsor company reimbursement up to a maximum of 90 days. The selection of antiretrovirals will be investigator-chosen.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing ~~specific~~ **reimbursement for** post-study treatment.

Section 6.10.1 Meals and Dietary Restrictions

Previous section number 6.12

Rationale for change

This section was updated to remove language around meal provisions (language consistent for an in-patient trial). As this is an out-patient trial, it will be up to trial site to arrange when/how meals are provided during a subject's participation in the trial. The section 'Lifestyle and/or Dietary Restrictions' had no content described under it. The sections 'Meals and Dietary Restrictions' and 'Alcohol, Caffeine and Exercise' has been moved as sub-sections under the section 'Lifestyle and/or Dietary Restrictions', as the sub-sections are related to this section.

Revised Text

Second Bullet

Doses will be given in the fed state (light breakfast), following overnight fasting (>10 hours). ~~Lunch will provided ≥4 hours after the dose; water will be allowed ad libitum throughout.~~

Section 6.10.2 Alcohol, Caffeine and Exercise

Previous section number 6.13

Rationale for change

Adjustments were made to these lifestyle habits to eliminate restrictions on use of tobacco products, reduce restrictions on alcohol use and to allow occasional and light exercise during study treatment.

Revised Text

Alcohol, Caffeine~~, Tobacco~~ and Exercise

- ~~Subjects should refrain from alcohol for 48 hours before screening and then for 48 hours prior to admission and baseline assessments (on Day 1). Alcohol is then not permitted for the duration of the treatment period (through Day 10) and until the final follow-up visit.~~
- ~~Use of tobacco products is not allowed from screening until after the final follow-up visit~~
- ~~Subjects will~~ **During the study alcohol consumption should be limited to the following:**
  - **An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.**
- Subjects ~~will~~ **should** abstain from strenuous exercise ~~for 72 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities~~ during ~~studies (e.g., watch television, read).~~**the treatment period.**

Section 6.11 Contraception

Rationale for change

This section was updated to clarify that use of oral contraceptives are permitted during the study.

Revised Text

Second paragraph

Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. ~~**There**~~ **Although use of oral contraceptives is permitted,** t~~T~~here is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.

Section 6.12 Concomitant Medications and Non-Drug Therapies

Previous section number 6.14

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous section 6.12) and 'Alcohol, Caffeine and Exercise' (previous section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 6.10), the section has been re-numbered.

Deleted Text

- ~~Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 for each treatment period. A positive result will lead to exclusion from the remainder of the study.~~
- ~~The Principal Investigator must be informed as soon as possible about any medications taken from the time of screening until the subject is discharged from the study. Over-the-counter medications will not be permitted during the treatment period except as needed to treat an AE. If medication is needed, use should be restricted to 4 hours after dosing if possible.~~

Section 6.12.1 Permitted Medications and Non-Drug Therapies

Previous section number 6.14.1

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous Section 6.12) and 'Alcohol, Caffeine and Exercise' (previous Section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 10), the section has been re-numbered.

Revised Text

Addition of Second bullet

- **Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Subjects must notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications.**

Section 6.12.2 Prohibited Medications and Non-Drug Therapies

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous Section 6.12) and 'Alcohol, Caffeine and Exercise' (previous Section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 10), the section has been re-numbered.

Previous section number 6.14.2

Revised Text

- ~~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.~~
- **Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 and at additional timepoints throughout the study. A positive result will lead to exclusion from the remainder of the study.**

Section 7.1 Time and Events Table

Rationale for change

The Time and Events table was updated to remove the post-dose 12-lead ECG on Day 5, which remains in line with the FDA's guidance regarding days on which to perform post-dose (2 & 6 hours to capture near Tmax) ECGs. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Also minor clarifications were made and typographical errors were corrected.

Revised Text

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Informed Consent	X																
Review inclusion/exclusion	X		X														
Demography including height, weight and BMI	X																
Brief physical			X														
Medical/medication/ drug/alcohol history	X		X														
CDC Classification	X		X													X	X
Prior antiretroviral therapy	X																
12-lead ECG[3]	X		X			X	~~X~~			X		X	**X**	X		X	X
Holter (24 hr)	X																
Vital signs[4]	X		X			X	X			X		X		X		X	X
Drug screen	X		X			X						X				X	
Hepatitis B Surface antigen and hepatitis C antibody testing	X																
Serum or urine β-hCG (WoCBP only)	X		X														X
Clinical lab tests (inc troponin)	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Fasting lipid panel	X																X
AE assessment[5]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Con Medication Review	X		X	X	X	X	X			X	X	X	X	X	X	X	X
HIV-1 RNA PCR[6]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Lymphocyte subsets[7]	X		X										X				
Plasma for genotype/phenotype[8]			X			X	X			X			X			X	X
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		~~X~~**X**[14]
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														
~~**AE enquiry**~~[13]			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Telephone call to IVRS[13][14]	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Plasma for storage[15]			**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

1. Screening will occur within **14-**30 days prior to the first dose of study drug.
2. Table is set up for the weekend during dosing to occur on Days 6 and 7. If the weekend occurs on Days 5 and 6, perform all "Day 5" assessments on Day 7.
3. On Day 1, ECGs ~~(x2)~~ will be performed pre-dose , and then 1, 1.5, 2, 3, 4 and 6 hours post dose. The ~~pre-dose~~ ECGs should be performed at least 5 minutes apart and preferably within 1 hour prior to dose. On Days 4~~, 5~~ and 8, ECGs will be obtained prior to morning dosing and at 2, 4 and 6 hours post-dose. **To accommodate scheduling, serial ECGs collected on Days 4 and 8 may be performed ± 1 day.** On Day 10, ECGs ~~(x2)~~ will be performed pre-dose, and then 1, 1.5, 2, 3, 4 and 6 hours post dose. On Day 11, an ECG will be obtained prior to the 24-hour PK sample. **ECGs will be performed in triplicate at all timepoints.**
4. BP, RR, HR and temperature will be obtained at Screening (x1) and Day 1 pre-dose (x2). BP and HR will be obtained on Day 1 at 2 hours post-morning dose and on Days 4, 5 and 8 pre-dose. BP and HR will be obtained on Day 10 at pre-dose and 2 hours post-morning dose, and at **day 12 and** Follow-up **(Day 21)**.
5. Only SAEs related to study participation will be collected between screening and Day 1. **An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status.**
6. On Days 1-5 and 8-10 samples for HIV-1 RNA PCR collected before morning dose. On Days 1, 10 and 11 two samples for HIV-1 RNA PCR will be collected 5-30 minutes apart. **HIV-1 RNA PCR samples will also be collected on days 12, 14 & Follow-up (Day 21).**
7. Lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+and CD8+counts).
8. Blood samples for phenotype and genotype will be collected at pre-dose on Days 1, 4, 5 and 8 in the morning on Day 11 and at follow-up.
9. Serial plasma samples (2 mL) for determination of GSK2838232 will be collected on Day 1 and Day 10 at pre dose (within 15 minutes prior to dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 **(optional),** and 24 hours **(to occur on morning of Day 2** post-am dose and **in the morning on Day 11)** . Pre-dose PK samples (within 15 minutes prior to dose) will be taken on the mornings of Days 3, 4, 5, 8 and 9 and a single sample will be taken on Days 12 and 14.
10. Samples (2 x 0.5mL) of plasma for assessment of immunological markers at screen, baseline (pre-dose) and day 11
11. Subjects will receive a single dose of GSK2838232 and cobicistat each morning with a light breakfast meal and 240 mL of water from Day 1 to Day 10. Doses taken in the clinic will be administered after an overnight fast of at least 10 hours .On Days 6 and 7, doses will be self administered but confirmed by phone
12. PGx sample should be collected on Day 1.
13. ~~An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status~~
13. A screening/registration call should be made to the IVRS to register the subject at screening. An additional call will be made to document a screen failure. A randomization call should be made to the IVRS system approximately one week prior to scheduled Day 1. Note: The randomization call must be made in order to have study drug on site for Day 1. Additional calls will be made every day that the subject has a scheduled study visit to the clinic. If a subject terminates the study prematurely a call should be made to the IVRS
14. Only if early termination visits occur during the treatment period.
15. **Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally these samples will be used when needed, such as when samples are lost or arrive at the laboratory unevaluable.**

AE = Adverse event; CDC= Center for Disease Control and Prevention; ECG = Electrocardiogram; ET = Early termination; hCG = Human chorionic gonadotrophin; HIV = Human immunodeficiency virus; IVRS= Interactive Voice Response System; PCR = Polymerase chain reaction; PK=Pharmacokinetic.

Section 7.2 Visit Windows

Rationale for Addition

Visit/procedure windows were included to allow more flexibility with scheduling of assessments.

New Section

Screening (baseline to pre-dose): All screening assessments should take place within 14-21 days prior to the first dose. The screening visit window may be extended to 30 days upon discussion with the Medical Monitor (i.e.; subject has scheduling conflicts or any screening assessment needs to be repeated).

Days 4 and 8: Based on subject and clinic schedule, Day 4 and Day 8 serial (up to 6h post-dose) ECG assessments may be conducted ± 1 day.

Weekend(s): The T&E table is set up for study start (Day 1) to occur on a Monday and Days 6 and 7 to fall on the weekend. If the weekend occurs instead on Days 5 and 6, Day 5 assessments should be performed on Day 7. The study start (Day 1) may also be adjusted to allow visits with assessments to be conducted over the weekend based on subject and clinic schedule.

Assessments: The following applies to timing of procedures:

- **Window for assessments ≤ 4 h post-dose = ± 5 minutes**
- **Window for assessments >4 and <u>< 12 h post-dose = ± 15 minutes</u>**
- **Window for assessments ><u>12 h post-dose = ± 30 minutes</u>**

End of Treatment visit: should be within 14 days from last dose of study drug. If a subject is unable to return to the clinic for any reason site staff are encouraged to telephone the subject for assessment of adverse events.

Section 7.3.1 Holter Monitoring (Screening criteria)

After addition of new section before this section, the section numbers from this section until Sections under 7.0 are re-numbered using the next available section number.

Rationale for Change

Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirement to allow flexibility based on clinic and subject schedule.

Revised Text

The 24-hour Holter monitoring ~~should only~~ **will** be performed ~~at~~ **during the** Screening ~~after the subject has met all other inclusion criteria.~~ **period using a Holter monitoring device supplied by the Sponsor.**

Analysis of the Holter tapes will consider the following:

- Heart rate (brady**cardia** and tachycardia)

- Normal and aberrant beats
- Number of supraventricular contractions, premature atrial contractions, premature ventricular contractions, couplets, triplets, and ventricular tachycardias
- Atrio-ventricular conduction defects
- Atrial fibrillation and flutter

Section 7.5.1.1 Time period and Frequency for collecting AE and SAE information

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

Bullet 4

- All SAEs will be recorded and reported to ~~GSK~~ **Sponsor** within 24 hours, as indicated in Appendix 5, Section 12.5.

Section 9.3.2 Interim Analysis

Rationale for Change

Minor corrections and clarifications were made to this section.

Revised Text

An interim analysis of preliminary safety, tolerability, PK and antiviral activity will occur after subjects of Part A Cohort 1 complete their Day 13 visit. If ~~based on this review~~ the Cohort 1 dose is determined to be the highest dose **based on this review** (e.g**.,** the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects), the Bayesian posterior probability that the log10 viral load decline from baseline is greater than a cut-point will be calculated. If the Bayesian probability from Cohort 1 is less than 70%**,** this will provide ~~evidenceto~~ **evidence to** not move forward into Part B. Otherwise, the study team will review the data in order to make a dose selection decision for the subsequent Part B Cohorts. If the pharmacokinetic exposures after the 100 mg GSK2838232/cobi dose look similar to those obtained with 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) **GSK2838232** doses.

Maximum change and change from baseline in plasma HIV-1 RNA will be summarized by treatment or by assessment day. The proportion of subjects with plasma HIV-1 RNA <400 and <50 copies/mL will be summarized by treatment and assessment day. The analyses will be done for both PP and ITT exposed population if **the** two populations are not the same.

Section 10.3 Quality Control (Study Monitoring)

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

First Bullet

In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors **or designee** 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.

Section 10.5 Study and Site Closure

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

First Bullet

Upon completion or premature discontinuation of the study, the GSK monitor **or designee** 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.

Section 11 References

Rationale for Change

Have mentioned the references as per GSK style guide and template.

Revised Text

Elion R, Cohen C, Gathe J, Shalit P, Hawkins T, Liu HC, **et al**. ~~Mathias AA, Chuck SL, Kearney BP, Warren DR.~~ Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine.tenofovir df in the initial treatment of HIV infection. *AIDS*. 2011; 25:1881-1886.

Gallant JE, Koenig E, Andrade-Villaneuva J, Chetchotisakd P, deJesus E, Antunes F, Arastéh K, **et al**. ~~Moyle G, Rizzardini G, Fehr J, Liu Y, Zhong L, Callebaut C, Sewarcberg J, Rhee MS, Cheng AK.~~ Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV type 1-infected patients: week 48 results. *J. Infect. Dis.* 2013; 208-:32-39.

Kakuda TN, Opsomer M, Timmers M, Iterbeke K, Van De Casteele T, Hillewaert V, **et al.** ~~Petrovic R, Hoetelmans RMW.~~ Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. *J. Clin. Pharmacol.* 2009; 54:949-957.

Lalezari J, McCallister S, Gigliotti M, Cohen C, Elion R, **Brinson C,** et al. Safety and efficacy study of bevirimat (BVM) in heavily treatment experienced HIV+ patients identifies the target phase 3 study profile. ICAAC. 2008; Abstract: H891.

Martin DE, Blum R, Wilton J, Doto J, Galbraith H, **Burgess GL**, et al. Safety and pharmacokinetics of bevirimat (PA-457), a novel inhibitor of human immunodeficiency

virus maturation, in healthy volunteers. *Antimicrobial Agents and Chemotherapy.* 2007(b);Sep:3063-6.

Appendix 1 Abbreviations

Rationale for Change

The abbreviations used in the document are added to the list of abbreviations.

AIDS	~~Auto~~ Acquired immunodeficiency syndrome
BID	**Twice daily**
DDI	**Drug-Drug Interaction**
PPD	**Pharmaceutical Product Development**
QD	**Once daily**
RIBA	**Recombinant Immuno-Blot Assay**
~~t1/2~~**t½**	Terminal elimination half-life

12.10.2. AMENDMENT 2

Protocol Amendment 2 (24-MAY-2017) from the Protocol Amendment 1 (26-Apr-2017)

Where the Amendment Applies

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

List of Specific Changes: (**bold** indicates text added and ~~strikethrough~~ indicates text removed)

Summary of Protocol Amendment Changes with Rationale

Amendment 2 includes expansion of the eligible subject population to allow treatment experienced HIV-1 infected patients, in addition to treatment naive patients. Patients with a treatment history of a prior maturation inhibitor will still be ineligible. Slight modifications were made to include flexible language for enrolment into Part B to allow prioritization of one dose cohort or to open randomization into Part B cohorts in a parallel fashion. Also the upper limit of the BMI inclusion criteria was increased from 31 to 35 kg/m^2.

Minor clarifications, re-numbering of sections and correction of typographical errors were also made throughout this amendment.

Author (s)

Rationale for change A minor correction was made to this section.

A minor correction was made to this section.

Revised Text

PPD PCPS, GSK, ~~Collegeville~~**Upper Providence**, PA, US

Title Page

Rationale for change

The protocol title was updated to reflect the new subject population, which is no longer limited to treatment naive patients.

Revised Text

A Phase 2a, Multicenter, Randomized, Adaptive, Open-label, Dose Ranging Study to Evaluate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Cobicistat-boosted GSK2838232 Monotherapy Over 10 Days in HIV-1 Infected ~~Treatment-Naive~~ Adults

Synopsis

Rationale

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed). The reference to a parallel enrolment design for Part B was also removed to allow for prioritizing enrolment into any one dose cohort based on emerging data from Part A.

Revised Text

Second paragraph

Three clinical studies of GSK2838232 (n=53 healthy subjects) have been completed thus far. One study (Study 204953) ~~is on-going~~**completed at the end of 2016 and analysis of the data is ongoing**. Healthy subjects have received GSK2838232 or placebo in single or repeated dose designs, to a maximum single dose of 250 mg or repeated dose (for 11 days) of 200 mg QD, in combination with ritonavir (RTV).

Fifth paragraph

Study 204953 ~~is an on-going study and continues the~~**investigated the safety and PK of GSK2838232 in** single and repeat-dose**s** ~~exploration of safety and PK of GSK2838232~~as well as the suitability of a new, capsule formulation. Doses of up to 250 mg GSK2838232/100 mg RTV (as single doses) or 200 mg GSK2838232/100 mg RTV (QD for 11 days) were studied. ~~As of 26 October 2016, the study is ongoing with a cohort of subjects due to receive~~**The final cohort of the study assessed** unboosted GSK2838232 (200mg BID) for 11 days. **The study completed at the end of 2016 and the data analysis is ongoing.**

Seventh paragraph

The objective of Study 200911 is to understand the safety, PK and HIV antiviral profile of GSK2838232/cobicistat (GSK2838232/cobi) when given to HIV-infected, treatment naive, otherwise healthy adults. Approximately 10 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology, and PK data analysis, approximately 8 subjects will be enrolled in each of between two and four Cohorts in Part B~~, which will be a parallel group design~~.

Design, Treatment Arms and Duration

Rationale for change

This section was updated to reflect the new subject population, which is no longer limited to treatment naive patients.The reference to a parallel enrolment design for Part B was also removed to allow for prioritizing enrolment into any one dose cohort based on

emerging data from Part A. A reference to Study 205820 was also included as data from this planned study will provide additional information on unboosted GSK2838232.

Revised Text

First paragraph

Approximately 34 HIV-1 infected ~~treatment-naive~~ subjects will be enrolled overall.

Second paragraph

This study is a 10-day monotherapy, open-label, adaptive, dose ranging, repeat-dose study and will be conducted as two parts with an interim (go/no-go) analysis performed after Part A (Table 1). Part A, Cohort 1 will evaluate a safe and well-tolerated dose level of GSK2838232 that has been tested (with RTV) in prior Phase I studies and that targets a high inhibitory quotient (IQ) value. Following the completion of an interim analysis of those data and according to criteria defined later in the protocol, further cohorts of 8 subjects will then be studied in Part B in ~~a parallel design in~~ two or more cohorts (depending upon the data obtained in Part A).

Table 1 Study Design for 200911

	Part A: GSK2838232/cobi Once Daily x 10 days[1]		Part B: GSK2838232/cobi Once Daily x 10 days[1,2]		
Cohort	N	232 Dose (mg)	Cohort	N	232 Dose (mg)
1	10	100			
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B~~, which are planned to run in a parallel, randomized fashion~~. All doses will be given with 150 mg cobicistat.
2. Part B GSK2838232 doses are an illustration of the projected doses per cohort. The actual doses for each cohort **and number of cohorts** are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobi co-dosing) may be added (the maximum dose in Part B would **likely** not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] was lower in HIV infected subjects than in healthy subjects at the same dose level).

Fourth paragraph

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) was assessed **and Study 205820, which plans to evaluate GSK2838232 at a dose of 500mg once daily (QD)**.

Section 2.2.2.1 Clinical Summary of Safety

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed).

Revised Text

Fifth paragraph

In ~~ongoing~~Study 204953, there have been a small number of CV-related events of any sort: There have been no serious adverse drug reactions, and no clinically significant drug-related abnormal findings for 12-lead ECGs, vital signs, safety laboratory results (including cardiac troponin I), or telemetry. The following cardiovascular AEs were observed during the course of the study but were not considered to be caused by GSK2838232 exposure

Section 2.2.2.2 Study 204953 (completed); Pharmacokinetic Data

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed and analysis is ongoing).

Revised Text

Second paragraph

In addition, it evaluated the relative bioavailability of a single fasted dose of micronized API powder blend in capsules with RTV compared to powder-in-bottle for oral suspension with RTV and the effect of a normal fat meal on the bioavailability of a single dose of GSK2838232 in the capsule formulation with RTV. It will evaluate GSK2838232 exposure after repeated doses of unboosted GSK2838232 in the capsule formulation. Noncompartmental PK analysis was performed using scheduled sample times. ~~This~~**The** ~~study is~~**anaylsis of data from this study is** ongoing; preliminary results are presented.

Section 4.1 Overall Design

Rationale for change

This section was updated to reflect the new subject population, which is no longer limited to treatment naive patients.The reference to a parallel enrolment design for Part B was also removed to allow for prioritizing enrolment into any one dose cohort based on emerging data from Part A.

Revised Text

First paragraph

This is a Phase IIa, multicenter, open-label, adaptive dose ranging, study to evaluate the antiviral effect, safety, tolerability, and PK of GSK2838232/cobi monotherapy over 10 days in ~~ART-naïve~~ HIV-1 infected adults who are not currently receiving ART therapy. Subjects who have received any ~~ART (including prior MI)~~ **prior maturation ihibitor** therapy will not be eligible for this study. To minimize the number of subjects exposed to suboptimal doses, an adaptive and dose ranging design is applied in this study.

Study Design for 200911

GSK2838232/cobi Once Daily for 10 days[1,2]					
Part A			**Part B**		
Cohort 1	**Dose (mg)**	**Interim Analysis**	**Cohort**	**N**	**(mg)**
N=10	100				
			2	8	200
			3	8	50
			4	8	20

1 . Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B~~, which are planned to run in a parallel, randomized fashion~~. All doses will be given with 150 mg cobicistat.

2 . Part B doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobicistat co-dosing) may be added. (The maximum dose in Cohort B will **likely** not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] is lower in HIV-infected subjects than in healthy subjects at the same dose level).

Day 1 – Day 10: Dosing

Second paragraph

Serial, intensive blood PK samples will be collected on Day 1 (up to 24 hours post-morning dose) and Day 10 (up to 96 hours post-morning dose), and limited, single blood PK samples pre-morning doses on Days 3 through 9, except for the weekend. Subjects will be required to fast for 10 hours [overnight] prior to the morning check in on the intensive PK sampling days (Days 1 and 10). All dosing days will require co-administration of treatment with a light snack/meal per cobicistat labeling guidelines. All doses of study medication will be taken with 240 mL of water. Subjects will be required to stay in the clinic on Days 1 and 10 until all specified assessments are completed (**8-**12 hours post-dose). Following Day 10, subjects will be required to attend the clinic for follow up assessments including virological and PK blood sampling for up to 3 weeks.

Section 4.2 Type and Number of Subjects

Rationale for change

Minor clarifications were made to this section.

Revised Text

At least 34 subjects will be enrolled such that approximately 6-10 evaluable subjects complete a number of cohorts. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels as appropriate.

If subjects prematurely discontinue the study, additional~~replacement~~ subjects may be ~~randomised~~**randomized** and assigned to the same treatment cohort at the discretion of the Sponsor in consultation with the Investigator.

Section 4.3 Design/Dose Justification

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed).

Revised Text

Last paragraph

There is no *a priori* intention to study GSK2838232 unboosted, unless: i) following the preliminary analysis of Part A Cohort 1, there is such pronounced antiviral activity that it would seem the estimates of projected IQ are low, in which case GSK2838232 may be evaluated in a subsequent cohort unboosted, or ii) the data from ongoing **and planned healthy volunteer trial**s,~~Cohort 7 in~~ Study 204953 (~~planned,~~ GSK2838232 200 mg BID **unboosted**) **and Study 205820 (GSK2838232 500mg QD** unboosted**)** support it.

Section 4.3.3 Interim Analysis

Rationale for change

Minor clarifications were made to this section to allow for flexibility around selecting dose cohorts for Part B based on emerging data from Part A.

Revised Text

An evaluation of GSK2838232 safety, efficacy and PK data will be done after Part A Cohort 1, if the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects and the Bayesian probability from Cohort 1 is less than 70%, the study will not move forward into Part B, otherwise doses will be selected for evaluation in Part B. If pharmacokinetic exposure after the 100 mg GSK2838232/cobi dose is in the range of values observed after 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower

(20 mg **and/or**~~,~~ 50 mg) and higher (200 mg) doses. The highest dose tested in Part B will be selected to result in exposures similar to those seen with 200 mg/r in Study 204953.

Section 4.4.3 Overall Benefit:Risk Conclusion

Rationale for change

Minor clarifications were made to this section to provide clarification regarding Study 204953 (which is now completed).

Revised Text

To date, **115**~~53~~ healthy subjects have received GSK2838232 in **four**~~three~~ completed studies. ~~One study (204953) is ongoing (52 healthy subjects have completed this study so far).~~

Section 5 SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Rationale for change

This section was updated to reflect the new subject population, which is no longer limited to treatment naive patients.The reference to a parallel enrolment design for Part B was also removed to allow for prioritizing enrolment into any one dose cohort based on emerging data from Part A.

Revised Text

Second paragraph

Approximately 10-12 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology and PK data analysis, approximately 8 subjects will be enrolled in each of Cohorts 2-4 in Part B~~, which will be a parallel group design~~. Eligible patients are those who are **maturation inhibitor**~~ART~~-naïve and who are not currently receiving ART therapy.

Last paragraph

If subjects prematurely discontinue the study, additional subjects may be enrolled ~~as replacement subjects and assigned to the same treatment at the discretion of the Sponsor~~.

Section 5.1 Inclusion Criteria

Rationale for change

The inclusion criteria were updated to reflect the new subject population, which is no longer limited to treatment naive patients. Also the upper limit of the BMI inclusion criteria was increased from 31 to 35 kg/m^2.

Revised Text

5. Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening. ~~No current and no prior ART. (A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug).~~

~~5.~~**6. Antiretroviral treatment naive or ART-experienced (maturation inhibitor naive). No current ART (last dose completed at least 6 weeks prior to the first dose of study drug).** ~~(~~A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug~~)~~.

~~6.~~7. Body weight ≥ 50 kg (110 lbs.) for men and ≥45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-3~~5~~1.0 kg/m^2 (inclusive)

Section 6.2 Treatment Assignment

Rationale for change

A minor clarification was made to this section.

Revised Text

Subjects will be assigned to treatment (active) **groups** in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Section 6.4 Blinding

Rationale for change

Minor clarifications were made to this section.

Revised Text

This will be an open-label study. Treatment allocation **and GSK2838232 dose levels** in Part B will be **determined after the analysis of Part A data.** ~~randomised (to GSK2838232 dose level).~~

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase 2a, Multicenter, Randomized, Adaptive, Open-label, Dose Ranging Study to Evaluate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Cobicistat-boosted GSK2838232 Monotherapy Over 10 Days in HIV-1 Infected Treatment-Naive Adults

Compound Number: GSK2838232

Development Phase: IIA

Effective Date: 26-APR-2017

Protocol Amendment Number: 01

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N227852_00	2016-NOV-09	Original
2015N227852_01	2017-APR-26	Amendment No. 1
Amendment 1 includes minor updates to Inclusion-Exclusion (IE) criteria, including clarification on use of pre- or post-exposure prophylaxis, and removal of exclusionary requirements related to concomitant medications and tobacco and alcohol use during the study. Guidance around relevant habits is included in the Lifestyle section of the protocol and adjustments were made to reduce restrictions on these requirements. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirements. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Furthermore, the serial ECG collection (up to 6h post-dose) was removed on Day 5. Finally, the post-study care guidance was updated to include an option for subjects to receive reimbursement for marketed ART for a limited period after completion of study treatment and follow up. Minor clarifications, reformatting of tables, re-numbering of sections and correction of typographical errors were also made throughout this amendment.		

SPONSOR SIGNATORY

PPD

April 26, 2017

Brian Johns, PhD PPD Date

Vice President, HIV DPU

PPD

April 26, 2017

Etienne Dumont, MD Date

Project Physician Lead

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

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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): 116,094

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 200911

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

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 200911

Rationale

GSK2838232 is a novel human immunodeficiency virus (HIV-1) maturation inhibitor that is being developed for the treatment of HIV-1 in combination with other antiretrovirals.

Three clinical studies of GSK2838232 (n=53 healthy subjects) have been completed thus far. One study (Study 204953) is on-going. Healthy subjects have received GSK2838232 or placebo in single or repeated dose designs, to a maximum single dose of 250 mg or repeated dose (for 11 days) of 200 mg QD, in combination with ritonavir (RTV).

Study HMI116787 (completed November 2013) was the First Time in Human study of GSK2838232 and assessed safety and tolerability of escalating doses (5 mg to 100 mg), food effect, and the impact of steady-state ritonavir on GSK2838232 pharmacokinetics (PK). Following successful completion of 3-month toxicology studies in rat and dog in 2014, clinical studies 200912 and 200207 were initiated. These were double-blind, placebo-controlled, single (Study 200912) and repeat-dose (Study 200207) escalation studies to investigate the safety, tolerability, and PK of GSK2838232 alone and when co-administered with ritonavir 100 mg once daily (QD) for 8-11 days. Further assessment of an alternative formulation was also an objective in Study 200912.

Both studies were prematurely terminated/completed in March/April 2015 because of concerns over cardiovascular (CV) toxicity, in particular a clinical CV serious adverse event (SAE) whereby the Food and Drug Administrating (FDA) imposed a clinical hold. Following submission of long-term (6-month rat, 9-month dog) chronic toxicology data and follow up to the clinical SAE in November 2015, the hold was released in January 2016 and Study 204953 was initiated.

Study 204953 is an on-going study and continues the single and repeat-dose exploration of safety and PK of GSK2838232 as well as the suitability of a new, capsule formulation. Doses of up to 250 mg GSK2838232/100 mg RTV (as single doses) or 200 mg GSK2838232/100 mg RTV (QD for 11 days) were studied. As of 26 October 2016, the study is ongoing with a cohort of subjects due to receive unboosted GSK2838232 (200mg BID) for 11 days.

These studies have shown GSK2838232 with or without RTV to be well tolerated and, together with daily RTV dosing ("boosting"), demonstrate a PK profile suitable for progression to HIV patients in this Phase IIa proof of concept 10-day, monotherapy study design. However, potential concerns over protease resistance necessitate a change to a pharmacoenhancer without antiviral effects in this study of GSK2838232 monotherapy. Therefore, for Study 200911, cobicistat (Tybost,150 mg QD) will be substituted for RTV.

The objective of Study 200911 is to understand the safety, PK and HIV antiviral profile of GSK2838232/cobicistat (GSK2838232/cobi) when given to HIV-infected, treatment naive, otherwise healthy adults. Approximately 10 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology, and PK data analysis,

approximately 8 subjects will be enrolled in each of between two and four Cohorts in Part B, which will be a parallel group design.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate antiviral activity of GSK2838232/cobi in HIV-1 infected patients during 10 days of monotherapy.	• Change from baseline (Day 1) in plasma HIV-1 RNA
• To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days.	• Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments.
• To characterize the pharmacokinetics of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days.	• GSK2838232 PK parameters following dose administration, as follows: **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Secondary	
• To explore the relationship between GSK2838232 exposure and change in plasma HIV-1 RNA	• GSK2838232 PK parameters Day 10 AUC(0-τ), Cmax, Cτ with Day 11 HIV-1 RNA change from baseline
• To assess the immunologic effect of GSK2838232/cobi when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ cell count to Day 11
• To explore the relationship between GSK2838232 exposure and safety or immunologic parameters, if appropriate.	• GSK2838232 PK parameters on Day 10: AUC(0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count

Objectives	Endpoints
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate
• To estimate GSK2838232 accumulation and to assess attainment of steady state following administration of GSK2838232/cobi for 10 days in HIV infected subjects.	• **Accumulation:** GSK2838232 PK accumulation ratios (R): Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively • **Steady State:** pre-morning dose concentrations (C0) on Days 2 through 11
• To examine dose proportionality of GSK2838232 pharmacokinetic parameters following GSK2838232/cobi dosing for 10 days in HIV infected subjects.	• Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax, and Cτ at different dose levels for the assessment of dose proportionality
Note: Other exploratory objectives and endpoints will be specified in the RAP	

Design, Treatment Arms and Duration

Approximately 34 HIV-1 infected treatment-naive subjects will be enrolled overall.

This study is a 10-day monotherapy, open-label, adaptive, dose ranging, repeat-dose study and will be conducted as two parts with an interim (go/no-go) analysis performed after Part A (Table 1). Part A, Cohort 1 will evaluate a safe and well-tolerated dose level of GSK2838232 that has been tested (with RTV) in prior Phase I studies and that targets a high inhibitory quotient (IQ) value. Following the completion of an interim analysis of those data and according to criteria defined later in the protocol, further cohorts of 8 subjects will then be studied in Part B in a parallel design in two or more cohorts (depending upon the data obtained in Part A).

The totality of this data will provide a full dose-response of GSK2838232 over a wide dose range to explore the safety and PK/pharmacodynamics (PD) relationship of GSK2838232 in HIV-1 infected subjects and facilitate choice of doses for Phase IIb studies.

Table 1 Study Design for 200911

	Part A: GSK2838232/cobi Once Daily x 10 days[1]		Part B: GSK2838232/cobi Once Daily x 10 days[1,2]		
Cohort	N	232 Dose (mg)	Cohort	N	232 Dose (mg)
1	10	100			
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B, which are planned to run in a parallel, randomized fashion. All doses will be given with 150 mg cobicistat.
2. Part B GSK2838232 doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobi co-dosing) may be added (the maximum dose in Part B would not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] was lower in HIV infected subjects than in healthy subjects at the same dose level).

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) was assessed.

Subjects in both parts will have a screening visit within 30 days prior to first dose and a follow-up visit 7-14 days after the last dose. Maximum duration of study participation will be approximately 6 weeks.

HIV Drug Resistance: Following cessation of GSK2838232/cobi dosing for 10 days, there will be prolonged exposure to waning plasma concentrations of GSK2838232, because of the long t½ (i.e., in the "tail" of the PK profile). However, based on in vitro resistance passage data with GSK2838232 [and unlike with many other ARV therapies], there appears to be a limited likelihood of developing maturation resistance mutations in HIV-infected subjects due to its virologic profile.

Analysis

The primary objectives of this study are to investigate the safety, tolerability, PK and antiviral activity of 10 days repeated doses of GSK2838232/cobi in HIV-1 infected otherwise healthy subjects. Descriptive summaries will be provided for safety, PK, and HIV viral load data.

2. INTRODUCTION

GSK2838232 is a novel human immunodeficiency virus (HIV)-1 maturation inhibitor (MI) that is being developed for the treatment of HIV-1 infection in combination with other antiretrovirals (ART).

2.1. Study Rationale

This 'proof of concept (PoC)' open-label study is being conducted to characterize the acute antiviral activity, pharmacokinetics (PK), the relationship between PK and antiviral activity, and safety of GSK2838232 given with 150 mg once daily (QD) cobicistat (GSK283232/cobi), administered across a range of doses over 10 days in HIV-1 infected patients. A two part adaptive and dose ranging design is to be applied in this study. Data from this study will be utilized to select doses for further studies in Phase IIb.

2.2. Brief Background

Combination antiviral therapy with inhibitors of HIV protease, integrase, entry and reverse transcriptase (RT) has demonstrated significant improvement in acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality over the last 10-15 years. Emerging multi-class drug resistant viral strains and long-term toxicities warrant development of new classes of antiretroviral therapies targeting various parts of the HIV-1 viral life cycle [Wainburg, 2010]. The inhibition of maturation of HIV-1 is a novel target for drug development, distinct from viral protease RT or integrase [Saxena, 2012; Qian, 2009]. HIV maturation is the final cleavage step of the capsidSp1 (transcription factor) polyprotein that generates the functional capsid p24 protein. This mechanism of action results in accumulation of the uncleaved p25 protein with subsequent improper assembly of the HIV core, resulting in a non-infectious virion. Gel-based mechanism of action studies suggest that compound GSK2838232 acts as a maturation inhibitor. Western Blot analysis shows inhibition of capsid-Sp1 cleavage and accumulation of p25 in the presence of GSK2838232.

Prior validation of this target was demonstrated with the HIV maturation inhibitor known as bevirimat (BVM; [Martin, 2007a; Martin, 2007b; Martin, 2008; NORVIR, 2013]). BVM reached Phase II studies in HIV patients; however, only modest reductions in plasma HIV-1 ribonucleic acid (RNA) concentrations were observed in Phase IIa monotherapy studies [Mahmood, 2006; Martin, 2007] and a pattern of polymorphic (differential) antiviral activity [Wainburg, 2010] led to termination of BVM development. The average decrease from baseline to Day 14 plasma HIV-1 ribonucleic acid (RNA) was 0.54 and 0.70 log10 copies/mL for 200 mg and 300 mg twice daily regimens (Table 2); all subjects achieved plasma BVM concentrations above the in vitro EC90. Responders, classified based on 5 polymorphisms in HIV-1 gag (at positions 369, 370, and 371), achieved an average 1.15 log10 copies/mL reduction in plasma HIV-1 RNA, while an average 0.17 log10 copies/mL reduction was achieved for non-responders.

Table 2 Summary of Bevirimat Antiviral Response and PK in a 14-day Monotherapy Study in HIV-infected Adults

BVM dosage regimen	Mean (SD) viral load change from baseline to Day 14	[2]IQ	Plasma BVM [1]Cmin (μg/mL)	Plasma BVM [1]Cmax (μg/mL)	Plasma BVM [1]AUC(0-τ) (μg.h/mL)
200 mg BID (N=14)	-0.54 (0.64)	1.70	46 (41, 51)	58 (53, 64)	632 (571, 699)
300 mg BID (N=18)	-0.70 (0.77)	2.67	72 (65, 80)	91 (84, 99)	973 (890, 1064)

1. Cmin, Cmax, and AUC reported as geometric mean (95% CI).
2. IQ=geometric mean Cmin/in vitro EC90; reported EC90=27 μg/mL; all subjects achieved IQ ≥1.

AUC(0-τ) = Area under the concentration-time curve over the dosing interval; BVM = Bevirimat; CI = Confidence interval; Cmax = Maximum plasma concentration; Cmin = Minimum plasma concentration; EC90 = 50% protection against resistant mutant HIV infection; IQ = Inhibitory quotient; SD = Standard deviation.

Early clinical data for BMS955176, a second generation maturation inhibitor, have been recently presented [Nowicka-Sans, 2015]. In a 10-day monotherapy trial in HIV-infected patients, plasma HIV-1 RNA was reduced at doses of between 40 mg and 120 mg QD. All doses were well tolerated. The maximum change, seen between 10 and 12 days after starting dosing, was about 1.5 log10, which is substantially better than the effect demonstrated with BVM and may indicate the maximum expected clinical effect of inhibiting this viral target.

Although BMS955176 is currently in Phase II studies in HIV-infected patients, there are no maturation inhibitors approved for the treatment of HIV infection. The uncertainties of early drug development and continuing need for novel ART, especially for heavily treated/experienced HIV-infected persons, support continued compound development. GSK2838232's low nanomolar in vitro potency against multiple HIV-1 gag polymorphisms and broader spectrum across multiple HIV-1 subtypes indicates it has utility in this setting.

2.2.1. Preclinical Summary

Nonclinical pharmacology

Virology

GSK2838232, in vitro, is an inhibitor of HIV maturation by preventing the cleavage of the HIV gag structural subunit p25 to p24. GSK2838232 is a potent antiviral agent with a mean 50% maximal inhibitory concentration (50% maximal inhibitory concentration [IC50]) value of 1.6 nM (range: 0.8 to 4.3 nM) when tested in a panel of 26 HIV-1 isolates with various polymorphic gag genotypes in peripheral blood mononuclear cells (PBMCs), suggesting that GSK2838232 can inhibit a broad spectrum of HIV isolates. In another PBMC assay, GSK2838232 showed potent antiviral activity in 59 of 60 isolates with IC50 values ranging from 0.22 to 5.1 nM. GSK2838232 also inhibited HIV-1 strains containing the consensus Sp1 QVT region or the V370A polymorphism in MT4 cells (IC50 = 0.73 to 0.81 nM).

In an MT2 cell-based assay utilizing recombinant viruses harboring gag and protease from subjects before and after a protease inhibitor (PI) based regimen, GSK2838232 inhibited 12 of 15 viruses with a mean IC50 value of 1.7 nM (range = 0.4 to 3 nM). The remaining 3 viruses were not inhibited by GSK2838232 up to the top concentrations tested at 400 nM. There was no correlation of PI sensitivity and susceptibility to GSK2838232. GSK2838232 resistance mutations were selected for by serial passage of virus in a SupT1 cell-based assay with increasing concentrations of GSK2838232. In the lab strain NL4-3 and gag/protease recombinant viruses, the resistance mutation A364V arose and resistance confirmed by site-directed mutagenesis. This resistance mutation maintains susceptibility to other classes of anti-retrovirals including PIs and non-nucleoside RT inhibitors.

GSK2838232 was tested in vitro in combination with two marketed PIs, atazanavir and darunavir. Using a dose-wise additivity model, GSK2838232A showed additive anti-viral activity with both PIs.

Secondary Pharmacology

In a secondary pharmacology study, GSK2838232 was tested against a panel of receptors, ion channels and transporters and demonstrated no significant effect (IC50 of ≤1 μM). It is important to note that the selectivity for antiviral activity of GSK2828232 compared to all tested off-target activities was >100-fold, and the potential for organ toxicity was characterized in the nonclinical toxicology studies (see below).

In safety pharmacology studies in male rats, there were no hemodynamic changes or neurobehavioral effects following single oral doses up to 300 mg/kg. A single oral dose of GSK2838232 at 30 mg/kg or 300 mg/kg produced reversible increases in respiratory tidal volume (32% and 36%, respectively) and derived minute volume (17% and 26%, respectively) at 6 hours after dosing. These doses did not produce any effect on respiratory rate, airway resistance or body temperature. There were no respiratory effects in rats given 5 mg/kg (mean maximum plasma concentration [C_{max}] 0.12 μg/mL; AUC_{0-24} 1.0 μg.h/mL based on Day 1 of the 4-week repeat dose study). These findings were not considered to suggest a safety concern in humans.

GSK2838232 at the maximum feasible concentration, limited by solubility, of 4.09 μM (3.31 μg/mL) caused no inhibition of human ether-a-gogo related gene (hERG) tail current in Human Embryonic Kidney 293 cells stably transfected with hERG cDNA, indicating a low probability for interaction at the hERG channel.

In conscious telemetered male dogs (n=4), a single oral dose of GSK2838232 at 60 mg/kg (C_{max} 0.59 μg/mL; AUC_{0-24} 8.7 μg.h/mL based on Day 1 exposure data from the 4-week oral repeat dose toxicity study) was associated with one episode of non-sustained ventricular tachycardia in one dog lasting ~1.2 seconds. There were no effects on arterial pressures, heart rate, or electrocardiogram (ECG) interval durations. An investigative safety pharmacology cardiovascular study was conducted in telemetered dogs given 60 mg/kg/day for 4 weeks with serial monitoring by echocardiography, cardiac biomarkers, qualitative and quantitative electrocardiology, microscopy, and transmission electron microscopy (TEM) of the heart.

There were no changes in echocardiography endpoints, ECG intervals, ECG waveforms, arterial pressures, heart rates, serum cTpnI, N-terminal prohormone of brain natriuretic peptide (NTproBNP), or in heart tissue as assessed by TEM. With routine microscopy, one treated dog had a single focus of degeneration/necrosis of the tunica media (moderate) in an extramural artery and another treated dog had localised, mixed-cell inflammation (mild) along the epicardium of the coronary groove. Both changes have been reported in normal beagles and were considered of uncertain relationship to treatment in the absence of changes in any other structural or functional cardiovascular endpoints. The 28-day exposures were similar to the previous 4-week toxicity study in dogs: the C_{max} range at 60 mg/kg/day in this investigative safety pharmacology study was 0.542 to 2.00 µg/mL and range of AUC_{0-24} was 6.04 to 35.7 µg.h/mL. In subsequent repeat-dose studies in dogs treated for up to 9 months with up to 70 mg/kg/day, no changes were evident in cardiac biomarkers (including cTpnI and NTproBNP), functional (including ECG waveform) or structural (including microscopic evaluation) cardiovascular endpoints at slightly higher exposures than those achieved than in previous studies. The end of the 9-month study, gender averaged C_{max} at 70 mg/kg/day was 1.95 µg/mL and AUC_{0-24} was 38.8 µg.h/mL. These studies support an absence of GSK2838232-related functional or structural effects on the heart in preclinical testing. The No Observed Adverse Effect Level (NOAEL) was established at 20 mg/kg/day (on the basis of mild hepatic findings) with an associated area under the curve at 24 hours (AUC24) of 16.2 µg.hr/mL and Cmax 0.847 µg/mL.

Pharmacokinetics and product metabolism in animals

The PK of GSK2838232 were investigated in the mouse, rat, and dog. The oral bioavailability of GSK2838232 was low to moderate (~6% to 40%) depending on the species and formulation. Plasma and blood clearance were low and the volume of distribution at steady state was high relative to total body water. The half-life of GSK2838232 was short in the mouse and rat, but moderate in the dog. Systemic exposure of GSK2838232 generally increased in a less than dose-proportional manner. In rats, there were no differences in systemic exposure between single and repeat-dose administration, or between males and females. In a 7-day study in dogs, systemic exposures were generally similar between males and females and after single and repeat dosing; however, in a 4-week study, systemic exposures were higher in females than in males in the high-dose group (60 mg/kg/day) and higher after repeat dosing than after a single dose. The distribution of radioactivity in male pigmented rats following a single oral administration of [^{14}C] GSK2838232 at a target dose level of 20 mg/kg showed radioactivity was rapidly absorbed and widely distributed throughout the body with all tissues, except the brain and spinal cord. There were no tissues that retained detectable levels of radioactivity at 28 days post dose. In a bile duct canulated rat study, 30% of the administered dose was excreted in the bile as an acylglucuronide. In the same study, unchanged drug and metabolites were eliminated primarily in the bile and feces, while a mean of <1% of the dose was eliminated in urine.

In vitro, GSK2838232 is highly protein bound (>99.9%) and has low passive permeability. In vivo evidence suggests active uptake of GSK2838232 by transporters in the rat liver.

After single oral doses of 5, 100, or 300 mg/kg, the average liver to plasma ratio was 51, 17, and 10, respectively. After 7 days of dosing at 30, 100, or 300 mg/kg/day, liver to blood ratios ranged from 10 to 16.

In the 13-week repeat dose studies in dogs given 35 mg/kg BID (70 mg/kg/day), heart tissue collected at necropsy had GSK2838232 concentrations 2.5 to 5-times higher than the 24-hour post-dose plasma concentrations, similar to the previous 4-week CV investigative findings. In the 13-week repeat dose studies in rats given 300 mg/kg/day, heart tissue collected at necropsy had GSK2838232 concentrations approximately 3 times higher than the 24-hour post-dose plasma concentrations, similar to the previous 7-day findings. Overall GSK2838232 did not appear to be highly concentrated in heart tissue after repeat dosing and suggests that accumulation upon chronic dosing is unlikely.

Routes of metabolism identified in liver microsomal incubations and rat, dog, and human hepatocytes were N-dealkylation, oxidation, oxidative deamination, and glucuronidation, alone or in combination, with no human-specific metabolites detected. N-dealkylated products and glucuronidation were observed in rat plasma and the bile. In general, in vitro metabolite profiles of the nonclinical species and human were qualitatively similar, such that all metabolites of [^{14}C] GSK2838232 observed in human hepatocyte incubations were observed in rat and/or dog. Minor to trace levels of potential aldehydes metabolites formed as a result of N-dealkylation and oxidative deamination were observed in rat, dog and humans.

GSK2838232 did not show evidence for glutathione adduct formation in rat or human liver microsomes. Data from pooled human liver microsomes along with recombinant cytochrome P450 (CYP) enzymes suggest that in vitro the oxidative metabolism of GSK2838232 was primarily mediated by CYP3A4. Preliminary in vitro investigations showed GSK2838232 did not inhibit CYP1A2, 2C9, 2C19, 2D6, 3A4 and was not a metabolism-dependent inhibitor of CYP3A4. No drug interaction risk was identified for co-administrated substrates of UGT1A1, 1A3, 1A6, 1A9, 2B7, and 2B15, OAT1, OAT3, OATP1B1, OATP1B3 or OCT2 at a clinical dose of 200 mg GSK2838232/ritonavir (predicted Cmax 0.32 μM). Extrapolation of the clinical risk (using FDA and EMA regulatory guidance) did indicate a risk for GSK2838232-mediated inhibition of UGT1A4 and of gut contributions of CYP3A4, P-gp, and BCRP at the same clinical exposure; however, the potential for clinically significant interactions via these mechanisms is predicted to be low (<2 fold change in AUC). GSK2838232 did show weak induction of CYP3A4 enzyme activity. However, based on the maximum predicted plasma concentrations and high protein binding, the potential for clinically significant drug interactions through CYP3A4 induction by GSK2838232 appears to be low.

The inclusion of cobicistat as a CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is unlikely to produce a significantly different profile of GSK2838232 ADME (and therefore systemic exposure); however, there have been no preclinical studies conducted with GSK2838232 and cobicistat to date.

Toxicology

GSK2838232 administered by oral gavage in repeat dose studies up to 6 months duration resulted in no adverse treatment-related effects in rats given up to 300 mg/kg/day QD.

In dogs given up to 70 mg/kg/day (35 mg/kg/day BID), adverse liver effects were noted at this dose in the 9-month repeat dose study. Though isolated, low grade changes in heart rate and cardiac troponin I (cTnI) had been noted in 4-week toxicity studies in rats and dogs; however, there were no treatment-related structural or functional cardiovascular changes in studies of 3 months and greater duration as assessed by echocardiography, ECG, microscopy, and cardiac biomarkers, indicating an absence of GSK2838232-related functional or structural effects on the heart in preclinical testing.

Only non-adverse treatment-related changes were noted in the definitive 6-month rat study, which included occasional salivation in animals given 300mg/kg/day and minimal clinical pathology changes without histologic correlates (transient clinical chemistry changes at ≥5 mg/kg/day and reversible urine chemistry changes at 300 mg/kg/day). The NOAEL in this study was considered to be 300 mg/kg/day (mean AUC[0-t] 21.3 μg.h/mL, mean Cmax 1.77 μg/mL [Week 26 values for males and females combined]).

As noted above, dogs given GSK2838232 at 70 mg/kg/day for 9 months had minimal to moderate pigmentation (consistent with bile) with minimal to mild mixed cell infiltration in the liver and isolated mild increases in alanine aminotransferase (ALT) activity. These findings were considered adverse, but were reversible after the 6-week off-dose period. The NOAEL for this dog study was considered to be the mid-dose level of 20 mg/kg/day (mean AUC[0-t] 16.2 μg.h/mL, mean Cmax 0.847 μg/mL [Week 39 values for males and females combined]).

Data from genotoxicity assessments suggest that GSK2838232 does not present a genotoxic hazard to humans.

During discussions with the FDA regarding the resolution of the clinical hold, the Agency recommended that the sporadic cardiovascular changes observed in the early (1-month) rat GLP study at the highest dose level (300 mg/kg/day) should be considered when defining the NOAEL and establishing a safe dose of GlaxoSmithKline (GSK) for the initiation of this study protocol. Accordingly, for the initial PK studies, the reference dose level of 30 mg/kg/day in the 1-month rat study was initially used to define the NOAEL and therefore the values for fold cover at maximum projected mean exposure and Cmax in human subjects were lower, at >2.5-fold. However, based on the cumulative clinical safety data through Cohort 5 of Study 204953, the designated NOAEL for the most sensitive species (i.e., 20 mg/kg/day in the 9-month dog study based on liver endpoints) is currently used for assessing fold-cover for projected clinical dosing in this study**.**

The inclusion of cobicistat as a CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is unlikely to produce a significantly different profile of GSK2838232 ADME (and therefore systemic exposure and toxicity); however, there have been no preclinical studies conducted with GSK2838232 and cobicistat to date.

Full details of non-clinical and clinical data may be found in the current Investigator's Brochure (IB) [GSK Document Number 2012N151889_03].

2.2.2. Clinical Summary of Safety and Pharmacokinetics

To date, GSK2838232 has been evaluated in three completed clinical studies with or without ritonavir (RTV) (GSK2838232/r). A fourth study (204953) completed late 2016 and data analysis is ongoing. Full details of the clinical results can be found in the Investigator's Brochure.

2.2.2.1. Clinical Summary of Safety

As of November 2016 fifty-three subjects had been exposed to GSK2838232 in 3 completed studies. One study (204953) completed in late 2016 and the analysis of results are ongoing (63 subjects were exposed to GSK2838232/r or placebo so far in this study). Overall, drug-related adverse events have been few and mild, and included headache, dizziness, fatigue, nausea, and palpitations and anxiety. Similarly, treatment-emergent laboratory abnormalities have also been few and mostly grade 1. There have been no discernible patterns, thus far, in terms of AEs or laboratory abnormalities.

One subject in study 200912 discontinued treatment with RTV due to an AE. A 47-year-old female who developed right upper quadrant abdominal pain, nausea and flatulence associated with grade 4 elevations in ALT and aspartate aminotransferase, and grade 2 elevations in total bilirubin (BIL). She was diagnosed with a common bile duct obstruction due to gallstones that spontaneously resolved. The Investigator assessed this AE as unrelated to study treatment.

Due to sporadic CV-related safety signals in the early animal studies (see Section 2.2.2), intense CV monitoring was in place for all four studies.

One AE occurred in HMI116787 that was initially considered a CV AE but after further evaluation was considered not to be of cardiac etiology. Two CV AEs occurred in 200207 that were initially considered possibly related to GSK2838232 exposure. However, further evaluation confirmed that there is a low likelihood that these events were due to GSK2838232 exposure. A summary of each event is provided in the IB.

In ongoing Study 204953, there have been a small number of CV-related events of any sort: There have been no serious adverse drug reactions, and no clinically significant drug-related abnormal findings for 12-lead ECGs, vital signs, safety laboratory results (including cardiac troponin I), or telemetry. The following cardiovascular AEs were observed during the course of the study but were not considered to be caused by GSK2838232 exposure:

- In Part 1A (Cohort 1), Period 2, a subject was withdrawn due to an AE (low hemoglobin) prior to GSK2838232 exposure Day -2. A replacement subject was brought in, but was not dosed with GSK2838232 or placebo because during the 2-day RTV run-in, on Day -1, the replacement subject met the stopping criteria for telemetry due to as brief occurrence of asymptomatic, NSVT prior to the first dose of GSK2838232 or placebo. Because the subject was excluded from the study prior to the first dose of investigational drug, the NSVT was not considered to be a serious and unexpected adverse drug reaction that would qualify for IND safety reporting.

- In Part 1A (Cohort 1), Period 3 (Period "3A" for the purpose of differentiating between 100 mg GSK2838232/r vs. 200 mg GSK2838232/r), one subject was discontinued prior to the first dose of study drug due to a series of cardiovascular findings (pre-ventricular contractions on telemetry). None of the findings were abnormal or atypical, but the investigator determined that this would not be a good etiology to have in a subject about to receive investigational drug. Because the event occurred prior to first dose of investigational drug, the finding was not considered to be due to GSK2838232 exposure.
- In Part 1A (Cohort 1), Period 3 (Period "3A" for the purpose of differentiating between 100 mg GSK2838232/r vs. 200 mg GSK2838232/r), one subject who had already been dosed on 2 previous occasions (with either GSK2838232 or placebo) was dosed for 2 days with RTV, and then on 05 May 2016 was dosed with either GSK2838232/r or placebo/r as scheduled. On the following day (06 May 2016), the subject experienced an asymptomatic, 6-beat run of NSVT, which was classified at the time as an SAE. Further monitoring, including continuous Holter monitoring revealed no further events. The subject had no troponin elevation throughout the study. After additional investigation it was determined that the NSVT had occurred after the subject had received placebo the previous day. Although the subject had received active on the two prior visits, the protocol allowed for sufficient washout between each dose. Therefore, because the subject had received placebo prior to experiencing the NSVT, the event was not considered to be due to GSK2838232 exposure or a serious and unexpected suspected adverse reaction that would qualify for IND safety reporting.
- In Part 2 (Cohort 6, 200mg/r), a 40 year old male enrolled in the study with no significant medical history experienced an asymptomatic ventricular triplet (NSVT) while asleep at 5:33am on Day 8 (of 11 days worth of dosing) approximately 21 hours after receiving 200 mg GSK2838232/r on the previous day at 8.25am. This event was noted by the site staff and the subject was assessed and found to have no associated clinical symptoms or complaints. The GSK medical monitor was notified. Because the subject was not symptomatic and this did not meet protocol-defined stopping criteria, the study was not unblinded at the time, and the subject was allowed to continue dosing. Dosing in the study is now complete and no further events have been noted. It was the assessment of the site PI and the GSK safety/monitoring team that a ventricular triplet can be seen in healthy volunteers on continuous Holter monitoring. Therefore neither the PI nor GSK considered this event to be a serious and unexpected suspected adverse reaction.

2.2.2.2. Study 204953 (completed); Pharmacokinetic Data

Study 204953 investigated the safety, tolerability, and PK of escalating doses of GSK2838232 as micronized API, with 100 mg RTV, initially as single doses and then as repeated doses for 11 days.

In addition, it evaluated the relative bioavailability of a single fasted dose of micronized API powder blend in capsules with RTV compared to powder-in-bottle for oral suspension with RTV and the effect of a normal fat meal on the bioavailability of a single dose of GSK2838232 in the capsule formulation with RTV. It will evaluate GSK2838232 exposure after repeated doses of unboosted GSK2838232 in the capsule formulation. Noncompartmental PK analysis was performed using scheduled sample times. This study is ongoing; preliminary results are presented.

Pharmacokinetic analysis was performed on GSK2838232 plasma concentration-time data using nominal time following single doses of 50, 100, and 250 mg in combination with RTV in Part 1A of Study 204953 (Table 3). On average, GSK2838232 Cmax values were reached 4-6 hours after dosing. Terminal half-life values ranged from 15 to 28 hours across the three dose levels. Overall, broad dose proportionality was observed for Cmax and AUC(0-∞) values with ascending single doses of GSK2838232 (50, 100, and 250 mg with 100 mg RTV).

Table 3 Summary of Preliminary Pharmacokinetic Parameter Values after Single Doses of GSK2838232 in Combination with 100 mg Ritonavir (Study 204953, Part 1A)

Dose (mg)	n	t½ (h)	tlag (h)	tmax (h)	Cmax (ng/mL)	AUC(0-∞) (ng.h/mL)
50	8	22.7 (17%) (17.2-28.5)	0.188 (138%) (0-0.5)	3.63 (41%) (2.5-6.0)	17.2 (43%) (8.7-27.9)	458.6 (33%) (210.6-662.0)
100	6	18.0 (14%) (15.8-22.3)	0.167 (155%) (0-0.5)	6.00 (59%) (2.5-12.0)	25.2 (20%) (17.5-31.5)	890.5 (20%) (619.1-1053)
250	5	17.3 (6.4%) (15.5-18.6)	0 (-) (0-0)	5.50 (71%) (2.0-12.0)	60.7 (23%) (40.8-73.1)	1731 (29%) (1222-2505)

Data are presented as mean (CV) (minimum-maximum).

Study 204953 Part 1B was an open label, 2x2+1 three-period, crossover design, evaluating the relative bioavailability of the micronized API GSK2838232 powder blend in capsules compared to the PiB reference formulation for the first two periods, with the assessment of food effect on the capsule formulation in Period 3.

The relative bioavailability of the micronized powder blend in 50 mg hand-filled capsules compared to the micronized API as PiB for oral suspension was assessed as 100 mg GSK2838232 single doses with 100 mg RTV after two pre-doses (48 h) in the fasted state in a randomized crossover design in 12 subjects in the first two periods of Part 1B of Study 204953. Preliminary geometric mean AUC(0-∞) and Cmax values were approximately 45% and 60% higher, respectively, after administration in the capsule formulation compared to oral suspension from PiB (Table 4).

Table 4 Preliminary Assessment of Relative Bioavailability of Capsule Formulation vs. Powder-in-Bottle Formulation of GSK2838232 (Study 204953, Part 1B)

Parameter	Test	Reference	n	Ratio of Geometric Least Square Means	90% CI of Ratio
AUC(0-∞)	Capsule	PiB	12	1.43	(1.194,1.702)
Cmax	Capsule	PiB	12	1.58	(1.312,1.900)

PiB = powder-in-bottle.

The potential food effect with the capsule formulation was assessed as 100 mg GSK2838232 single doses with 100 mg RTV after two pre-doses (48 h) in the fasted state and with a normal fat meal in a non-randomized crossover design (fasted in either Period 1 or 2, fed in Period 3). Eleven subjects provided data for both dietary conditions. Preliminary geometric mean AUC(0-∞) and Cmax values were approximately 60% higher after administration in the capsule formulation with a normal fat meal compared to the fasted state (Table 5).

Table 5 Preliminary Assessment of the Effect of a Normal Fat Meal on GSK2838232 Exposure when Administered as a Capsule Formulation with Ritonavir (Study 204953, Part 1B)

Parameter	n	Capsule – food Geometric mean	Capsule – fasted Geometric mean	Ratio of geometric means (food/fasted)
AUC(0-∞) (ng.h/mL)	11	2414	1539	1.57
Cmax (ng/mL)	11	76.9	47.2	1.63

Repeat dose PK parameter values in Study 204953 Part 2 were determined on Day 1 and Day 11 using nominal time in Part 2 of Study 204953 (Table 6). After the Day 11 dose of GSK2838232 with RTV, exposure (Cmax, AUC[0-τ]) appeared to increase proportionally with the increase in dose level with the PiB and capsule formulations.

Table 6 Summary of Preliminary Pharmacokinetic Parameter Values on Day 1 and Day 11 during Repeated Dosing of GSK2838232 in Combination with 100 mg Ritonavir (Study 204953, Part 2)

Dose (mg)	n	t½ (h)	tlag (h)	tmax (h)	Cmax (ng/mL)	AUC(0-τ) (ng.h/mL)	Cτ (ng/mL)
Study Day 1							
20 (PiB)	6	-	0.417 (49%) (0-0.5)	3.67 (11%) (3.0-4.0)	12.2 (47%) (5.8-20.8)	189.4 (40%) (83.7-284.4)	6.1 (39%) (2.5-8.9)
50 (PiB)	6	-	0.167 (155%) (0-0.5)	3.00 (51%) (2.0-6.0)	18.7 (40%) (9.0-25.9)	288.7 (39%) (138.6-380.2)	9.5 (35%) (5.1-12.6)
100 (capsules)	6	-	0.167 (155%) (0-0.5)	2.25 (23%) (1.5-3.0)	48.4 (32%) (28.1-69.6)	664.1 (31%) (422.5-932.7)	21.6 (33%) (12.8-29.3)
200 (capsules)	6	-	0.083 (245%) (0-0.5)	2.50 (25%) (2.0-3.5)	79.4 (38%) (50.8-125)	1124 (39%) (636.7-1794)	38.9 (36%) (21.7-58.6)
Study Day 11							
20 (PiB)	6	19.2 (16%) (15.1-24.2)	-	5.00 (32%) (2.5-6.0)	27.4 (38%) (11.3-40.4)	474.3 (31%) (214.3-613.2)	15.3 (30%) (7.1-19.2)
50 (PiB)	6	27.3 (52%) (15.2-50.4)	-	3.50 (46%) (1.5-6.0)	58.0 (24%) (40.9-78.0)	1113 (23%) (762.6-1459)	38.8 (29%) (24.5-51.7)
100 (capsules)	6	17.9 (18%) (15.2-23.7)	-	4.00 (40%) (2.5-6.0)	133 (23%) (94.7-164)	2492 (27%) (1624-3301)	81.7 (30%) (45.9-113)
200 (capsules)	6	-[1]	-	3.33 (45%) (1.5-6.0)	240 (38%) (127-368)	4389 (45%) (2095-7161)	151 (46%) (67.8-250)

Data are presented as mean (CV) (minimum-maximum).

1. Concentration data were available up to 24 h after the Day 11 dose, and t½ values were not calculated.

2.2.2.3. Overall Summary/Conclusions of PK data

The original formulation used in the first three studies with GSK2838232 (HMI116787, 200207, and 200912) was SDD. Data from Study 200912 demonstrated that a change to the API formulation of GSK2838232 was feasible for future clinical studies. Study 204953 utilized micronized API powder in a bottle as well as in a capsule. The capsule was shown to be a viable solid dosage form for subsequent studies. A more detailed summary of the data from Study 204953 is in Section 2.2.2.2.

- GSK2838232 SDD did not overall demonstrate significant escalation in exposure from an increase in dose from 100 mg to 200 mg in a cross-study comparison. The API PiB formulation showed a proportional increase in AUC and Cmax for a 2-fold dose escalation from 100 mg to 200 mg.
- The observed tmax of the API form was significantly increased over the SDD formulation (the API formulation also increased tlag relative to SDD).
- The bioavailability of the GSK2838232 API formulation was on average 30-50% of the bioavailability of SDD formulation, but there was a large observed range of relative intra-subject exposures (11-150%).
- Both 10 mg SDD and 20 mg API showed a 10-fold or greater increase in AUC with steady-state RTV (100 mg QD for 10 days) with a smaller (≤4-fold) increase in observed Cmax. The t½ of GSK2838232 increased from 15-18 hours to 34-42 hours in the presence of steady-state RTV, regardless of formulation.
- After single doses of 50 to 250 mg GSK2838232 with RTV, increases in Cmax and AUC(0-∞) values were broadly proportional to the increase in dose. On Day 11 after repeated daily 20 to 200 mg doses of GSK2838232 with RTV, increases in Cmax and AUC(0-τ) values appeared to be proportional to the increase in dose with the PiB and capsule formulations.
- The relative bioavailability of the micronized API powder blend in capsules with RTV was approximately 45%-60% higher than the bioavailability of the micronized API administered as oral suspension from PiB with RTV.
- Co-administration of the micronized API powder blend in capsules with RTV and a normal fat meal resulted in an approximately 60% increase in geometric mean Cmax and AUC(0-∞) values compared to the fasted state with RTV (Study 204953).
- Variability remains fairly constant across formulations and boosted versus unboosted at around 30%-40% (moderate-high).
- Projections of potential future efficacious boosted GSK2838232 API regimens suggest that doses of 20 to 200 mg GSK2838232 API co-administered with RTV will result in mean trough values of at least 3-fold above the derived 90% maximal inhibitory concentration (IC90) target value (5 ng/mL). Even if protein binding has more impact than envisaged and causes a 5-fold increase in IC90 as seen in some preclinical virology studies, the predicted troughs will still be significantly higher than the 5-fold shifted IC90 (25 ng/mL) at doses of 50 mg or higher with RTV.
- The average and maximum AUC/Cmax values observed at the maximum dose studied to date are below NOAEL values in preclinical chronic toxicology studies (6-month rat, 9-month dog).

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To evaluate antiviral activity of GSK2838232/cobi in HIV-1 infected patients during 10-days of monotherapy.	• Maximum decline from baseline (Day 1) in plasma HIV-1 RNA
• To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days.	• Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments.
• To characterize pharmacokinetics (PK) of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days	• GSK2838232 PK parameters following dose administration, as follows: **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Secondary	
• To explore the relationship between GSK2838232 exposure and change in plasma HIV-1 RNA	• GSK2838232 PK parameters Day 10 AUC(0-τ), Cmax, Cτ with Day 11 HIV-1 RNA change from baseline
• To assess the immunologic effect of GSK2838232/cobi when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ cell count to Day 11
• To explore the relationship between GSK2838232 exposure and safety or immunologic parameters, if appropriate.	• GSK2838232 PK parameters on Day 10: AUC(0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate

Objectives	Endpoints
• To estimate GSK2838232 accumulation and to assess attainment of steady state following administration of GSK2838232/cobi for 10 days in HIV infected subjects.	• **Accumulation:** GSK2838232 PK accumulation ratios (R): Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively • **Steady State:** pre-morning dose concentrations (C0) on Day 2 through 11
• To examine dose proportionality of GSK2838232 PK parameters following GSK2838232/cobi dosing for 10 days in HIV infected subjects.	• Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax and Cτ at different doses levels for the assessment of dose proportionality
Note: Other exploratory objectives and endpoints will be specified in the RAP	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIa, multicenter, open-label, adaptive dose ranging, study to evaluate the antiviral effect, safety, tolerability, and PK of GSK2838232/cobi monotherapy over 10 days in ART-naïve HIV-1 infected adults who are not currently receiving ART therapy. Subjects who have received any ART (including prior MI) therapy will not be eligible for this study. To minimize the number of subjects exposed to suboptimal doses, an adaptive and dose ranging design is applied in this study.

This study consists of a screening visit, a 10-day treatment period, and follow-up evaluations for 2 weeks following last dose.

Screening will be performed as the patients are identified, within 30 days of the first dose of study drug. Eligible HIV-1 infected subjects will receive study treatments for 10 days.

Study Design for 200911

GSK2838232/cobi Once Daily for 10 days[1,2]					
Part A			**Part B**		
Cohort 1	**Dose (mg)**	**Interim Analysis**	**Cohort**	**N**	**(mg)**
N=10	100				
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B, which are planned to run in a parallel, randomized fashion. All doses will be given with 150 mg cobicistat.
2. Part B doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobicistat co-dosing) may be added. (The maximum dose in Cohort B will not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] is lower in HIV-infected subjects than in healthy subjects at the same dose level).

After successfully completing screening evaluations, the first cohort will enroll 10 subjects to receive the 100 mg GSK2838232/cobi dose. Following interim analysis of Cohort 1, if warranted, Cohorts 2-4 will each enroll 8 subjects to receive a range of GSK2838232/cobi doses.

Day 1 – Day 10: Dosing

Subjects will report to the clinic for outpatient visits in the morning on Days 1 through 10 during the treatment period, except for the weekend (Days 6 and 7). Subjects will arrive each day prior to administration of the morning dose for safety and lab assessments, including HIV-1 RNA blood draws, as described in the Time and Events Table (Section 7.1). Subjects will begin receiving study drug in the morning of Day 1.

Serial, intensive blood PK samples will be collected on Day 1 (up to 24 hours post-morning dose) and Day 10 (up to 96 hours post-morning dose), and limited, single blood PK samples pre-morning doses on Days 3 through 9, except for the weekend. Subjects will be required to fast for 10 hours [overnight] prior to the morning check in on the intensive PK sampling days (Days 1 and 10). All dosing days will require co-administration of treatment with a light snack/meal per cobicistat labeling guidelines. All doses of study medication will be taken with 240 mL of water. Subjects will be required to stay in the clinic on Days 1 and 10 until all specified assessments are completed (12 hours post-dose). Following Day 10, subjects will be required to attend the clinic for follow up assessments including virological and PK blood sampling for up to 3 weeks.

Subjects will be given morning doses on Days 1 through 10 (except for the weekend) in the clinic. Weekend morning doses (Days 6 and 7) will be packaged and sent home for self-administration. After Day 11, the subjects will return frequently for assessments including blood draws for PK and HIV viral load. A diary card will be used to monitor dosing adherence.

Follow-up Visits:

Subjects will return to the clinic on Days 11, 12, 14 (±1 day), and 21 (±1 day) for PK and measurement of HIV-1 RNA levels, viral genotype/phenotype and safety assessments as shown in the Time and Events Table (Section 7.1).

4.2. Type and Number of Subjects

At least 34 subjects will be enrolled such that approximately 6-10 evaluable subjects complete a number of cohorts. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels as appropriate.

If subjects prematurely discontinue the study, additional replacement subjects may be randomised and assigned to the same treatment cohort at the discretion of the Sponsor in consultation with the Investigator.

4.3. Design/Dose Justification

The fastest track to establishing antiviral potential of any novel HIV drug is to study a short course of monotherapy in HIV infected subjects. There is precedent for this across a number of classes of ART drugs.

Uncertainties over the impact of protein binding on the activity of GSK2838232 and the inherent potency of inhibiting the HIV maturation process as a target remain key objectives for the GSK2838232 program. This two-part adaptive design will allow an early understanding of the potential of GSK2838232 in combination with cobicistat (and by implication, RTV), while not exposing HIV-infected subjects to longer courses of what may be suboptimal doses and possible development of resistance.

Early clinical studies have indicated that in order to achieve reasonable IQ values likely to be associated with antiviral efficacy, GSK2838232 will need to be boosted with a pharmacoenhancer, such as RTV or cobicistat (in common with many CYP3A4 substrates).

There is no *a priori* intention to study GSK2838232 unboosted, unless: i) following the preliminary analysis of Part A Cohort 1, there is such pronounced antiviral activity that it would seem the estimates of projected IQ are low, in which case GSK2838232 may be evaluated in a subsequent cohort unboosted, or ii) the data from Cohort 7 in ongoing Study 204953 (planned, GSK2838232 200 mg BID unboosted) support it.

4.3.1. GSK2838232 with Ritonavir

In Study HMI116787, a single dose of 10 mg GSK2838232 (SDD) given after 10 days of RTV 100 mg daily dosing (to steady state) demonstrated an increase in overall exposure (AUC) and Cmax by an average of 10.8- and 2.6-fold, respectively, compared to 10 mg GSK2838232 alone. Terminal phase half-life also increased from approximately 20 hours to 34 hours. This effect was presumably the result of an inhibition of a CYP3A4-mediated pathway. Studies 200912 and 200207 also indicated the utility of RTV in boosting GSK2838232 concentrations.

These data indicate the viability of studying a number of GSK2838232+RTV regimens in this PoC study. Predicted exposures following different GSK2838232 doses with steady-state RTV are presented in Table 7, based on the results of linear regression analyses of the preliminary Day 11 data in Study 204953 (dose levels of 20 to 200 mg) and assuming no significant differences in PK (ADME) between HIV-infected subjects and healthy subjects.

Table 7 Predicted Mean Steady-State GSK2838232 AUC(0-24), Cmax, and IQ, Following Repeated Dose Administration + RTV with Fold Cover to NOAEL

Dose (mg)	Projected AUC24 (ng.h/mL)[1]	Fold cover to NOAEL Dog[2]	Projected Cmax (ng/mL)[1]	Fold cover to NOAEL Dog[2]	IQ[3]
20+RTV	451	36	24	35	3.1
50+ RTV	1127	14	61	14	7.7
100+ RTV	2253	7.2	122	6.9	15
150+RTV	3380	4.8	183	4.6	23
200+RTV	4506	3.6	244	3.5	31

1. Predicted mean values based on linear regression analyses of preliminary Day 11 data in Study 204953.
2. Lowest NOAEL, 20 mg/kg/day obtained from 9-month study in dogs (AUC24 16200 ng.h/mL and Cmax 847 ng/mL)
3. Mean IQs derived from predicted Cτ/IC90 (with target of 5 ng/mL).

Cτ = Pre-dose (trough) concentration at the end of the dosing interval, IQ= inhibitory quotient.

The IQ following 20 mg to 200 mg GSK2838232/r QD is predicted to be >3 to >30-fold above the minimal target value (5 ng/mL) which was derived from preclinical virological assessment as 4 × EC50. No protein binding adjustment has been made because there was a minimal (≤5 fold) shift in assays where the effect of protein was assessed. If protein binding has more impact than anticipated, it is possible that the target Cmin value is approximately 25 ng/mL. In that scenario, projected IQ values at 200 mg/r QD would still be >5.

4.3.2. GSK2838232 with Cobicistat

There have been no preclinical or clinical studies with GSK2838232 and cobicistat to date; however, a review of the literature indicates that pharmacoenhancement of drugs that are known to have dominant CYP3A metabolic pathways is similar with either RTV or cobicistat [Kakuda, 2009; Elion, 2011; Gallant, 2013]. Thus, the use of cobicistat as the CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is expected to produce a similar profile of GSK2838232 ADME (and therefore systemic exposure). The pharmacokinetic data available after Part A Cohort 1 will confirm this assumption.

4.3.3. Interim Analysis

An evaluation of GSK2838232 safety, efficacy and PK data will be done after Part A Cohort 1, if the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects and the Bayesian probability from Cohort 1 is less than 70%, the study will not move forward into Part B, otherwise doses will be selected for evaluation in Part B. If pharmacokinetic exposure after the 100 mg GSK2838232/cobi dose is in the range of values observed after 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) doses. The highest dose tested in Part B will be selected to result in exposures similar to those seen with 200 mg/r in Study 204953.

4.4. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2838232 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.4.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2838232		
Cardiovascular	Pre-clinical studies have shown the following findings: elevated heart rates, an isolated episode of non-sustained ventricular tachycardia and minimal to mild, sporadic troponin I elevations in dogs. A subsequent investigative cardiovascular study in telemetered dogs treated for 4 weeks did not replicate these effects. Isolated microscopic cardiovascular changes were noted (focal extramural arteritis and localized epicardial inflammation), however these changes were considered of uncertain relationship to GSK2838232 because similar findings occur at low incidence in normal beagles and there were no GSK2838232-related functional changes by telemetry and echocardiography, or changes in cTpnI and NTproBNP. In addition there was no correlation between histologic changes and plasma exposure or heart tissue concentrations of GSK2838232. 3, 6 and 9 month toxicology studies in rat and dog did not demonstrate any evidence of cardiovascular injury or impact on cardiovascular function. In the four GSK2838232 studies conducted so far there was no pattern of cardiovascular changes of clinical significance related to GSK2838232 and no clinically significant abnormality in electrocardiogram values other than the two SAEs documented and discussed. Review of published bevirimat preclinical and clinical safety data indicates no significant toxicities or AEs of interest, other than a 30% incidence of gastrointestinal symptoms (including diarrhea). There were no significant cardiovascular AEs reported in published clinical studies.	Subjects will be clinically monitored for any signs of myocardial injury (chest pain, shortness of breath, pain with inspiration), elevated heart rate or arrhythmias. Samples for the assessment of troponin will be taken. Baseline EKG and Holter (to use for screening and for later comparisons if needed) Exposures of GSK2838232 will be closely monitored in the clinical study so as to not exceed pharmacokinetic stopping criteria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cobicistat (Tybost)		
General	The cobicistat label includes the following information: TYBOST decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating TYBOST In one study investigating cobi+(atazanavir and tenofovir DF/emtricitabine) vs RTV+(atazanavir and tenofovir DF/emtricitabine), a higher frequency of reports of jaundice (6% and 3%) and ocular icterus (4% and 2%) were reported in the cobi group compared to the RTV group. Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides have been observed. The implications of these findings are unknown. The vast majority of available safety data has been obtained in combination studies with other ART. There are no warnings of obvious cobicistat-related adverse events or safety concerns.	Subjects will be closely monitored for any signs or symptoms potentially associated with cobicistat administration, in particularchanges in serum creatinine and liver chemistry.
HIV-1 Infection/Patient population		
HIV Resistance Propensity for co-meds and possible Drug-Drug Interactions (DDIs)	HIV Drug Resistance to unique mechanism Recognize HIV patients have a higher chance of comorbidities/diseases and a risk of taking a medicine or product contraindicated in the study	Closely monitor HIV viral load and genotypic resistance Strict adherence to protocol criteria around concurrent meds

4.4.2. Benefit Assessment

This study in HIV-1 infected but otherwise healthy subjects is a 10-day monotherapy design. It is anticipated that all subjects receiving GSK2838232 will experience anti-HIV effects whereby their (blood) HIV viral titres are reduced, until administration stops and the viral load returns to baseline levels. There is no expected longer term anti-HIV benefit to administration of GSK2838232. Participation in this study contributes to the process of developing GSK2838232 and other new therapies for the treatment of HIV infection.

4.4.3. Overall Benefit:Risk Conclusion

To date, 53 healthy subjects have received GSK2838232 in three completed studies. One study (204953) is ongoing (52 healthy subjects have completed this study so far).

Subjects have received single doses up to 200 mg SDD alone (studies HMI116787 and 200912), 250 mg API in combination with RTV (204953), and then in repeated daily doses of up to 50 mg SDD alone (200207) for 5 days or 200 mg in combination with RTV (204953) for 11 days.

There have been two cardiovascular SAEs reported from clinical studies where the subject was receiving GSK2838232 to date (one in 200207, one in 204953). Neither is thought likely to be due to GSK2838232.

There have been no other withdrawals due to drug-related AEs and no trends relative to laboratory toxicity. One subject was withdrawn in Part 1A of 204953 because of low haemoglobin lab values, thought unrelated to study drug or study procedures.

With respect to CV effects, with the exceptions noted, there have been no clinically significant changes in troponin, heart rate, blood pressure, ECG, or telemetry monitoring.

Subjects will also be at risk for AEs from cobicistat use and will be monitored closely for such events.

Given the preclinical profile and the clinical profile to date, the overall risk to HIV-1 infected but otherwise healthy subjects at the proposed GSK2838232 doses (with or without cobicistat) for 10 days is predicted to be low. Mean exposures at the highest dose studied are not projected to exceed NOAEL values obtained in chronic toxicology studies, further reducing potential risk.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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.

Approximately 10-12 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology and PK data analysis, approximately 8 subjects will be enrolled in each of Cohorts 2-4 in Part B, which will be a parallel group design. Eligible patients are those who are ART-naïve and who are not currently receiving ART therapy.

Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels or configurations (e.g., GSK2838232 alone).

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment at the discretion of the Sponsor.

5.1. Inclusion Criteria

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

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy (other than HIV infection) male or female as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. Defined as no other chronic medical conditions and taking no chronic medications.
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.
4. A creatinine clearance >80 mL/min as determined by Cockcroft-Gault equation [Cockcroft, 1976] CLcr (mL/min) = (140 – age) * Wt / (72 * Scr) (times 0.85 if female) where age is in years, weight (Wt) is in kg, and serum creatinine (Scr) is in units of mg/dL.
5. Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening. No current and no prior ART. (A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug).

WEIGHT
6. Body weight ≥ 50 kg (110 lbs.) for men and ≥45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive)

SEX

7. Male or Female
 	
A female subject of reproductive or non-reproductive potential is eligible to participate if she is not pregnant (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test at screening and prior to first dose), not lactating, and at least one of the following conditions applies:
 	
Reproductive potential:
 	
Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. They will be counselled on safer sex practices
 	
There is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.
 	
Fertile females, who have an established, long-term lifestyle of sexual abstinence, or only same sex partners, require no other means of birth control.
 	
Non-reproductive potential:
 	
• Pre-menopausal females with one of the following:
  • Documented tubal ligation
  • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  • Hysterectomy
  • Documented Bilateral Oophorectomy
• Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
 	
Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until one week after the last dose of study medication.
 	
a. Vasectomy with documentation of azoospermia.
 	
b. Male condom plus partner use of one of the contraceptive options below:
  • Contraceptive subdermal implant that meets the SOP effectiveness criteria

including a <1% rate of failure per year, as stated in the product label

- Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
- Oral contraceptive, either combined or progestogen alone or Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

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.

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

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Alanine aminotransferase (ALT) and BIL >1.5xupper limit of normal (ULN; isolated BIL >1.5xULN is acceptable if BIL is fractionated and direct BIL <35%).
2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); HBV and/or HCV positive.
3. Subjects who have any other chronic medical condition, including CV, respiratory, neurologic, psychiatric, renal, gastrointestinal (GI), oncologic, rheumatologic, or dermatologic
4. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.

CONTRAINDICATIONS
5. 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.
RELEVANT HABITS
6. Chronic marijuana or use of other elicit medications (cocaine, heroin) is an exclusion criteria.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
7. Presence of hepatitis B surface antigen (HBsAg), positive (confirmed by Recombinant Immuno-Blot Assay [RIBA]) hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
8. Screening or baseline cardiac troponin I greater than the 99% cutoff (>0.045 ng/mL by the Dimension Vista CTNI assay).
9. A positive pre-study drug/alcohol screen.
10. Prior history of receiving an HIV maturation inhibitor
11. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.
12. 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).
13. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
14. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 30 days of study drug administration or anticipated need for such treatment within the study.
15. Treatment with immunomodulating agents (such as systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (such as hydroxyurea or foscarnet) within 30 days of study drug administration.
16. An active Center for Disease Control and Prevention (CDC) Category C disease except cutaneous Kaposi's sarcoma not requiring systemic therapy during the trial.
17. Treatment with any vaccine within 30 days prior to receiving study medication.
18. Exclusion Criteria for 24-Hour Screening Holter: • Any symptomatic arrhythmia (except isolated extra systoles). • Sustained cardiac arrhythmias (such as atrial fibrillation,flutter or supraventricular tachycardia (≥10 seconds) • Non-sustained or sustained ventricular tachycardia (defined as ≥3 consecutive

ventricular ectopic beats).

- Any conduction abnormality including but not specific to left or complete bundle branch block, atrioventricular [AV] block, high grade or complete heart block Wolff-Parkinson-White [WPW] syndrome etc.).
- Sinus Pauses >3 seconds.

19. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<45 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
*QTc interval	>450 msec	

*The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in 200911 will be Fridericia's formula.

- *Note: A heart rate from 100 to 110 beats per minute (bpm) can be rechecked by ECG or vitals within 30 minutes to verify eligibility.*
- Evidence of previous myocardial infarction (Does not include ST segment changes associated with repolarization).
- Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], WPW syndrome).
- Sinus Pauses >3 seconds.
- Any significant arrhythmia which, in the opinion of the principal investigator OR GSK medical monitor, will interfere with the safety for the individual subject.
- Non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats).

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 any SAEs.

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:

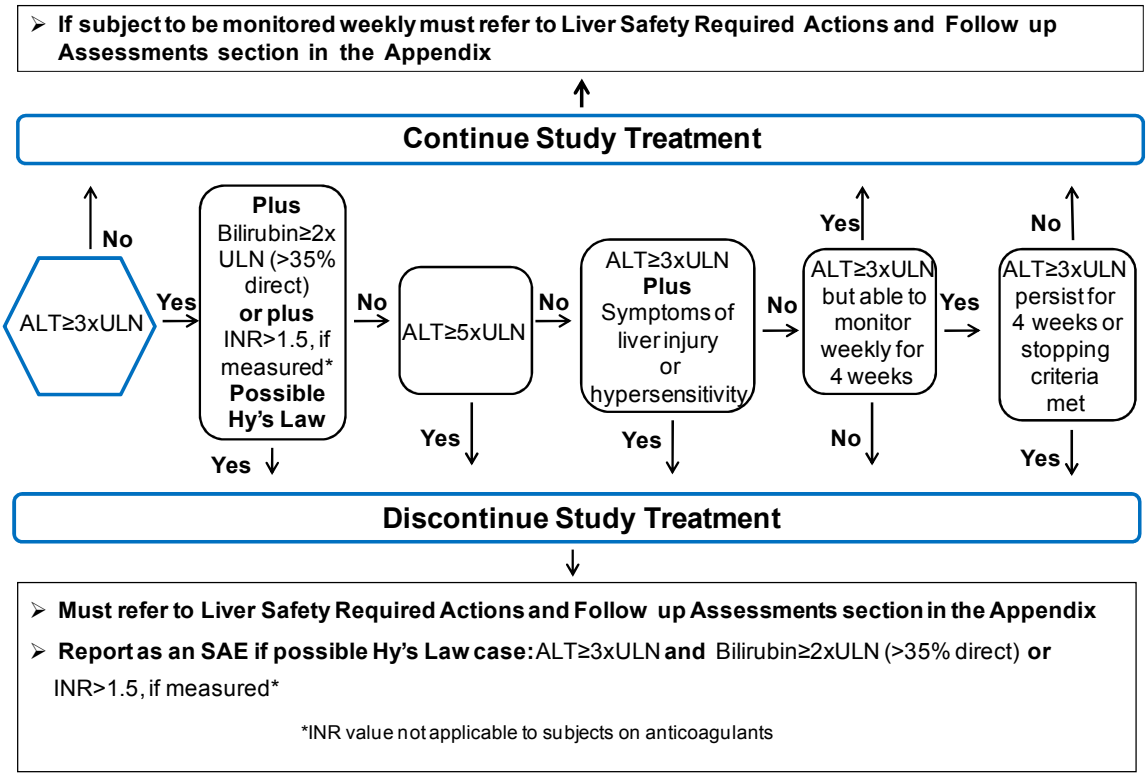
- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where 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 request has occurred in the site study records.

5.4.1. 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).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2, Section 12.2 and Section 12.3.

5.4.1.1. 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.

5.4.2. QTc Stopping Criteria

- The *same* 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.
  - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same 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 ECGs obtained over a brief (e.g., 5-10 minutes) recording period.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

5.5. Stopping criteria based on Adverse Events

Any grade 3 or higher treatment-related adverse events that occur in ≥2 subjects will be carefully reviewed and if considered clinically significant, dosing will be halted pending further discussion with the FDA. Any single treatment-related SAE will also trigger immediate evaluation and reporting processes in accordance with applicable regulations.

5.6. 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.

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Formulation description:	GSK2838232 powder blend in a capsule	Tablet
Dosage form:	Swedish orange, unmarked capsules (50 mg), and white, unmarked capsules (10 mg)	Orange, round, biconvex, film-coated tablets debossed with "GSI" on one side and plain faced on the other side providing 150 mg of cobicistat.
Unit dose strength(s)/ Dosage level(s):	50 mg capsule for 200 mg, 100 mg, 50 mg doses and 10 mg capsule for 20 mg doses	150 mg for 150 mg doses
Route/ Administration/ Duration:	Administered orally QD for 10 days	Administer orally, QD for 10 days

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Dosing instructions:	Administer with light meal and 240 mL of water.	Administer with light meal and 240 mL water.
Manufacturer/ source of procurement:	GSK	Gilead
Method for individualizing dosage:	Capsules supplied in high-density polyethylene bottles for individualized dosing by the clinic	Tablets supplied in bulk containers for individualized dosing by the clinic

6.2. Treatment Assignment

Subjects will be assigned to treatment (active) in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

6.3. Planned Dose Adjustments

Following the interim analysis of safety, virology and PK data from the first cohort of subjects in Part A, the option to adjust dose levels from those described exists. No dose will be administered that has an associated projected mean AUC or Cmax value higher than the most conservative NOAEL obtained from the chronic toxicity studies (i.e., from the 9-month dog toxicity study described in Section 2.2.1).

6.4. Blinding

This will be an open-label study. Treatment allocation in Part B will be randomised (to GSK2838232 dose level).

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for capsule/tablet storage and dispensing will be detailed in a Study Specific Technical Agreement/Memo or Pharmacy Manual, which will be accompanied by a Quality Agreement.

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.
- A Material Safety Data Sheet/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.

6.7. Compliance with Study Treatment Administration

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.

When subjects self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed through querying the subject during the site visits and documented in the source documents and case report form (CRF). A record of the number of study treatment(s) dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK2838232 >200 mg+cobicistat within a 28-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose; however, in the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK2838232 can no longer be detected systemically (at least 10 days for GSK2838232)
- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

- 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.

6.9. Treatment after the End of the Study

Subjects receiving GSK2838232 may opt to receive marketed antiretrovirals after the completion of 10 days of GSK2838232 dosing and study follow-up visits (through Day 21) eligible for sponsor company reimbursement up to a maximum of 90 days. The selection of antiretrovirals will be investigator-chosen.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing reimbursement for post-study treatment.

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice from 7 days prior to the first dose of study medication until after the final dose.
- Doses will be given in the fed state (light breakfast), following overnight fasting (>10 hours).

6.10.2. Alcohol, Caffeine and Exercise

- During the study alcohol consumption should be limited to the following:
    - An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.
- Subjects should abstain from strenuous exercise during the treatment period.

6.11. Contraception

Female subjects can be of childbearing or non-child bearing potential.

Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. Although use of oral contraceptives is permitted, there is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.

Females of reproductive potential, who have an established, long-term lifestyle of sexual abstinence, or only same sex partners, require no other means of birth control.

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until one week after the last dose of study medication:

1. Vasectomy with documentation of azoospermia. 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.

OR

2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

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.

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

- Acetaminophen at doses of ≤2 grams/day or NSAIDs are permitted for use any time during the study and their use documented in the CRF. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required.
- Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Subjects must notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications.

6.12.2. Prohibited Medications and Non-Drug Therapies

- Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 and at additional timepoints throughout the study. A positive result will lead to exclusion from the remainder of the study.

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 (Section 7.1), 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. In overview, subjects will be screened, begin dosing and then continue assessments through and for up to 2 weeks after the completion of dosing.

The following points must be noted:

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

    1. 12-lead ECG
    2. vital signs
    3. blood draws.

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

7.1. Time and Events Table

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Informed Consent	X																
Review inclusion/exclusion	X		X														
Demography including height, weight and BMI	X																
Brief physical			X														
Medical/medication/ drug/alcohol history	X		X														
CDC Classification	X		X													X	X
Prior antiretroviral therapy	X																
12-lead ECG[3]	X		X			X				X		X	X	X		X	X
Holter (24 hr)	X																
Vital signs[4]	X		X			X	X			X		X		X		X	X
Drug screen	X		X			X						X				X	
Hepatitis B Surface antigen and hepatitis C antibody testing	X																
Serum or urine β-hCG (WoCBP only)	X		X														X
Clinical lab tests (inc troponin)	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Fasting lipid panel	X																X
AE assessment[5]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Con Medication Review	X		X	X	X	X	X			X	X	X	X	X	X	X	X
HIV-1 RNA PCR[6]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Lymphocyte subsets[7]	X		X										X				
Plasma for genotype/phenotype[8]			X			X	X			X			X			X	X
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		X[14]
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Telephone call to IVRS[13]	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X
Plasma for storage[15]			X	X	X	X	X			X	X	X	X	X	X	X	X
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

1. Screening will occur within 14 - 30 days prior to the first dose of study drug.
2. Table is set up for the weekend during dosing to occur on Days 6 and 7. If the weekend occurs on Days 5 and 6, perform all "Day 5" assessments on Day 7.
3. On Day 1, ECGs will be performed pre-dose , and then 1, 1.5, 2, 3, 4 and 6 hours post dose. The ECGs should be performed at least 5 minutes apart and preferably within 1 hour prior to dose. On Days 4 and 8, ECGs will be obtained prior to morning dosing and at 2, 4 and 6 hours post-dose. To accommodate scheduling, serial ECGs collected on Days 4 and 8 may be performed ± 1 day. On Day 10, ECGs will be performed pre-dose, and then 1, 1.5, 2, 3, 4 and 6 hours post dose. On Day 11, an ECG will be obtained prior to the 24-hour PK sample. ECGs will be performed in triplicate at all timepoints.
4. BP, RR, HR and temperature will be obtained at Screening (x1) and Day 1 pre-dose (x2). BP and HR will be obtained on Day 1 at 2 hours post-morning dose and on Days 4, 5 and 8 pre-dose. BP and HR will be obtained on Day 10 at pre-dose and 2 hours post-morning dose, and at day 12 and Follow-up (Day 21).
5. Only SAEs related to study participation will be collected between screening and Day 1. An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status.
6. On Days 1-5 and 8-10 samples for HIV-1 RNA PCR collected before morning dose. On Days 1, 10 and 11 two samples for HIV-1 RNA PCR will be collected 5-30 minutes apart. HIV-1 RNA PCR samples will also be collected on days 12, 14 & Follow-up (Day 21).
7. Lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+and CD8+counts).
8. Blood samples for phenotype and genotype will be collected at pre-dose on Days 1, 4, 5 and 8 in the morning on Day 11 and at follow-up.
9. Serial plasma samples (2 mL) for determination of GSK2838232 will be collected on Day 1 and Day 10 at pre dose (within 15 minutes prior to dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 (optional), and 24 hours (to occur on morning of Day 2 post-am dose and in the morning on Day 11) . Pre-dose PK samples (within 15 minutes prior to dose) will be taken on the mornings of Days 3, 4, 5, 8 and 9 and a single sample will be taken on Days 12 and 14.
10. Samples (2 x 0.5mL) of plasma for assessment of immunological markers at screen, baseline (pre-dose) and day 11
11. Subjects will receive a single dose of GSK2838232 and cobicistat each morning with a light breakfast meal and 240 mL of water from Day 1 to Day 10. Doses taken in the clinic will be administered after an overnight fast of at least 10 hours .On Days 6 and 7, doses will be self administered but confirmed by phone
12. PGx sample should be collected on Day 1.
13. A screening/registration call should be made to the IVRS to register the subject at screening. An additional call will be made to document a screen failure. A randomization call should be made to the IVRS system approximately one week prior to scheduled Day 1. Note: The randomization call must be made in order to have study drug on site for Day 1. Additional calls will be made every day that the subject has a scheduled study visit to the clinic. If a subject terminates the study prematurely a call should be made to the IVRS
14. Only if early termination visits occur during the treatment period.
15. Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally these samples will be used when needed, such as when samples are lost or arrive at the laboratory unevaluable.

AE = Adverse event; CDC= Center for Disease Control and Prevention; ECG = Electrocardiogram; ET = Early termination; hCG = Human chorionic gonadotrophin; HIV = Human immunodeficiency virus; IVRS= Interactive Voice Response System; PCR = Polymerase chain reaction; PK=Pharmacokinetic.

7.2. Visit Windows

Screening (baseline to pre-dose): All screening assessments should take place within 14-21 days prior to the first dose. The screening visit window may be extended to 30 days upon discussion with the Medical Monitor (i.e.; subject has scheduling conflicts or any screening assessment needs to be repeated).

Days 4 and 8: Based on subject and clinic schedule, Day 4 and Day 8 serial (up to 6h post-dose) ECG assessments may be conducted ± 1 day.

Weekend(s): The T&E table is set up for study start (Day 1) to occur on a Monday and Days 6 and 7 to fall on the weekend. If the weekend occurs instead on Days 5 and 6, Day 5 assessments should be performed on Day 7. The study start (Day 1) may also be adjusted to allow visits with assessments to be conducted over the weekend based on subject and clinic schedule.

Assessments: The following applies to timing of procedures:

- Window for assessments ≤ 4 h post-dose = ± 5 minutes
- Window for assessments >4 and < 12 h post-dose = ± 15 minutes
- Window for assessments >12 h post-dose = ± 30 minutes

End of Treatment visit: should be within 14 days from last dose of study drug. If a subject is unable to return to the clinic for any reason site staff are encouraged to telephone the subject for assessment of adverse events.

7.3. 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.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.3.1. Holter Monitoring (Screening criteria)

The 24-hour Holter monitoring will be performed during the Screening period using a Holter monitoring device supplied by the Sponsor.

Analysis of the Holter tapes will consider the following:

- Heart rate (bradycardia and tachycardia)
- Normal and aberrant beats
- Number of supraventricular contractions, premature atrial contractions, premature ventricular contractions, couplets, triplets, and ventricular tachycardias
- Atrio-ventricular conduction defects
- Atrial fibrillation and flutter

7.4. Efficacy

7.4.1. HIV-1 RNA Sampling

Plasma for quantitative HIV-1 RNA will be collected at timepoints listed in the Time and Events Table in Section 7.1. To reduce sample variability, two plasma HIV-1 RNA samples will be collected on Days 1, 10, and 11.

An HIV-1 RNA PCR assay with a lower limit of detection (LLOD) of 50 copies/mL (ultrasensitive assay) will be used for post-baseline assessments. An HIV-1 RNA PCR assay with a LLOD of 400 copies/mL (standard assay) will be used for screening and baseline assessments and will include a re-test with and ultrasensitive assay for all baseline values below the LLOD. An HIV-1 RNA PCR assay with a LLOD of 2 copies/mL (supersensitive assay) may be used for exploratory analysis.

7.4.2. Lymphocyte Subsets by Flow Cytometry

Whole venous blood samples will be obtained from each subject for the analysis of lymphocyte subsets by flow cytometry at the timepoints listed in the Time and Events Table in Section 7.1.

Details concerning the handling, labeling and shipping of these samples will be supplied separately.

7.5. 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.

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

The definitions of an AE or SAE can be found in Appendix 5, Section 12.5.

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

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.5.1.3), at the timepoints specified in the Time and Events Table (Section 7.1). An AE enquiry will be made at each visit, where subjects will be specifically asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to Sponsor within 24 hours, as indicated in Appendix 5, Section 12.5.
- 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 5

7.5.1.2. 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?”
- “Have you experienced any alteration in personality, behaviour, mood or any altered mental status?”

7.5.1.3. 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, and non-serious AEs of special interest (as defined in Section 12.5) 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 5.

7.5.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 (Section 12.5.3) and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

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

The following disease-related events (DREs) are common in subjects with HIV-1 infection and can be serious/life threatening:

- events or outcomes listed in the CDC Classification System for HIV-1 Infections (see Appendix 9; Section 12.8)
- sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a serious adverse event).

These events will be recorded on the DRE page in the subject's CRF using the HIV Associated Conditions eCRF. These DREs will be monitored by the medical monitor and study team on routine basis.

However, if any of the following conditions apply, then the event should be reported as an SAE using the standard process:

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject,
  or
- The Investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.
  or

- Death occurring for any reason during a study, including death due to a disease related event, will always be reported promptly.

If either of the above conditions is met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly to GSK.

7.5.1.6. Regulatory Reporting Requirements for SAE

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs 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.

7.5.2. Pregnancy

- Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until one week post study
- If a pregnancy is reported then the investigator should inform GSK within 24hrs of learning of the pregnancy and should follow the procedures outlined in Appendix 7, Section 12.6.

7.5.3. Physical Exams

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

7.5.4. Vital Signs

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

7.5.5. Electrocardiogram (EGC)

- Triplicate 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.5.6. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments as defined in the Tables below must be conducted in accordance with the SRM and Protocol Time and Events Schedule (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled 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 SRM. 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 SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory:

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered in the CRF.

Haematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed below.

Table 8 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**
Haematology	Platelet Count; RBC Count; Hemoglobin; Hematocrit *RBC Indices*: MCV; MCH *WBC count with Differential:* Neutrophils; Lymphocytes with T-cell subsets; Monocytes; Eosinophils; Basophils
Clinical Chemistry [1]	BUN; Creatinine; Glucose; Troponin I Potassium; Sodium; Bicarbonates AST (SGOT); ALT (SGPT); Alkaline phosphatise Total and direct bilirubin; Total Protein; Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]

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 12.2 and Section 12.3
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 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.

7.6. Pharmacokinetics

7.6.1. Blood Sample Collection

Blood samples for analysis of GSK2838232 concentrations will be collected at the time points indicated in Time and Events Tables (Section 7.1).

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.6.2. Sample Analysis

Plasma analysis will be performed by Covance, Madison under the control of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS, GlaxoSmithKline. Concentrations of GSK2838232 will be determined in plasma using the currently approved bioanalytical methodology.

Once the plasma has been analyzed for GSK2838232 any remaining plasma may be analyzed qualitatively for other circulating metabolites and these results would be reported under a separate PTS protocol.

Raw data will be archived at the Covance, Madison facility.

7.7. Biomarker(s)/Pharmacodynamic Markers

7.7.1. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide plasma for viral genotype and phenotype analysis, at the times listed in the Time and Events Table in Section 7.1. Details concerning the handling, labeling and shipping of these samples will be supplied separately.

Genotypic and phenotypic analyses will be carried out by Monogram Biosciences using their GAG/PR and PR/RT formats, in which PCR amplification is used to generate HIV cDNA products including the Gag and the PR and RT coding regions, respectively. Phenotypic analyses of the GAG/PR region will include susceptibility to GSK2838232 . Analysis will be done on Day 1 and Day 11 samples. In the case of rebound HIV-1 viral load, analysis will be completed on samples corresponding to time point of rebound occurrence.

7.8. Genetics

Information regarding genetic research is included in Appendix 4, Section 12.4.

7.9. Value Evidence and Outcomes

Not required.

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 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

The primary objectives of this study are to investigate the safety, tolerability, and antiviral activity of GSK2838232 administered as monotherapy in combination with cobicistat in HIV-1 infected subjects, over a 10 day treatment period. The antiviral activity will be assessed by estimating plasma HIV-1 RNA max change from baseline during the study.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size for this study is based primarily on feasibility to provide adequate precision for the estimations.

Based on data from the short term monotherapy study of BMS-955176 PoC (AI468002) study and assuming viral load values for individual subjects follow a log-normal distribution, 1000 trial simulations in Fixed and Adaptive Clinical Trial Simulation (*FACTS*) software were conducted from the distribution with mean of change from baseline viral load drop on log scale at 1.0 to 1.5 copies and SD=0.4 and sample sizes=10 for Part A. Using Bayesian calculation with non-informative priors for the mean and weakly informative priors for the error parameters, Normal (0, 100) for mean and Inverse Gamma (0.35, 0.0875) for error parameters, the posterior probability to achieve a cutpoint 1.2 log was calculated for each simulated trial, and percentage of the trials with

posterior probability of viral load<-1.2log drop given true mean) ≥70% were calculated and are shown below in Table 9.

Table 9 Percentage of the trials with posterior probability>=70% for Part A

True Mean	Cutpoint	Posterior Prob>=70%
1.0	1.2	1.4%
1.1	1.2	9%
1.2	1.2	29%
1.3	1.2	59%
1.4	1.2	83%
1.5	1.2	96%

An Emax model with functional uniform priors [Bornkamp, 2014] was conducted using simulated data combining Part A and Part B with all doses. Success is defined as a posterior probability of the highest dose to achieve a cutpoint 1.2 log reduction in viral load. This was calculated for each simulated trial and the percentage of the trials with posterior probability greater or equal to 70% were also calculated and are shown below (Table 10). The table lists different viral load drop scenarios. The last scenario assumes the flat drop for all doses are 0.5. This scenario reflects the null hypothesis of no treatment effect. In this scenario 0% of the trials achieve the pre-specified decision rule for success.

Table 10 Percentage of the trials with posterior probability ≥70%

Cutpoint	Posterior Prob≥	Part A+ Part B mean VL drop for doses 200, 100, 50, 20	Part A+ Part B
1.2	70%	1.5, 1.4, 1.2, 0	99%
		1.5, 1.4, 1.2, 0.5	96%
		1.5, 1.4, 1.0, 0.5	93%
		1.5, 1.3, 1.2, 0.5	86%
		0.5, 0.5, 0.5, 0.5	0%

9.2.2. Sample Size Sensitivity

Similar simulations in FACTS were conducted from the distribution with mean of change from baseline viral load drop on log scale at 1.5 copies and SD=0.4 or 0.6 and sample sizes of 6-8 or 10 for Part A. Using Bayesian calculation, the posterior probability to achieve a cutpoint 1.2 log (in Table 11) was calculated for each simulated trial, and percentage of the trials with posterior probability greater than or equal to 70% was calculated and are shown below.

Table 11 Percentage of the trials with posterior probability ≥70% for Part A

True Mean	Cutpoint	Posterior Prob≥	Std for log10 VL	N=6	N=8	N=10
1.5	1.2	70%	0.4	90%	94%	96%
			0.6	75%	81%	84%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Intent to Treat Exposed Population (ITT)
The ITT-Exposed Population is defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received at least 1 dose of treatment and at least one post-baseline HIV-1 RNA measurement. This will be the primary population for the final efficacy analysis for all active treatment groups.

Per Protocol Population (PP)
The Per Protocol Population is defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received all doses and all post-baseline HIV-1 RNA measurement, with exceptions of major protocol deviation.

Safety Population
The Safety Population is defined as all subjects who are enrolled into the study with documented evidence of having received at least 1 dose of randomized treatment.

Pharmacokinetic Population
The PK Population will include all subjects who receive GSK2838232 and undergo plasma PK sampling during the study. Subjects for whom a plasma PK sample is obtained and assayed will be included in the listing of plasma GSK2838232 concentration-time data. Results from samples collected from a subject with emesis occurring within 4 hours of the dose will not be considered as evaluable.

9.3.2. Interim Analysis

An interim analysis of preliminary safety, tolerability, PK and antiviral activity will occur after subjects of Part A Cohort 1 complete their Day 13 visit. If the Cohort 1 dose is determined to be the highest dose based on this review (e.g., the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects), the Bayesian posterior probability that the log10 viral load decline from baseline is greater than a cut-point will be calculated. If the Bayesian probability from Cohort 1 is less than 70%, this will provide evidence to not move forward into Part B. Otherwise, the study team will review the data in order to make a dose selection decision for the subsequent Part B Cohorts. If the pharmacokinetic exposures after the 100 mg GSK2838232/cobi dose look similar to those obtained with 100 mg GSK2838232/r in

prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) GSK2838232 doses.

Maximum change and change from baseline in plasma HIV-1 RNA will be summarized by treatment or by assessment day. The proportion of subjects with plasma HIV-1 RNA <400 and <50 copies/mL will be summarized by treatment and assessment day. The analyses will be done for both PP and ITT exposed population if the two populations are not the same.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The 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 will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and %CVb for continuous variables, 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 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings. Complete details will be documented in the Reporting and Analysis Plan (RAP).

9.4.1.1. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library standards and data will be in CDISC format. No formal statistical analysis of the safety data will be conducted.

9.4.1.2. Efficacy Analyses

Both the PP and ITT Populations will be used for all efficacy analyses if there are dropouts. Plasma HIV-1 RNA max change and change from baseline during the study will be calculated for each subject on each assessment day.

Plasma HIV-1 RNA will be listed by treatment, subject, and assessment day and summarized by treatment and assessment day along with change from baseline.

Plots of mean and median plasma HIV-1 RNA actual and change from baseline data will be generated by treatment and assessment day.

- Plasma HIV-1 RNA change from baseline to the on-treatment nadir (maximum change) will be calculated for each subject and summarized by treatment.

Together, the data from Parts A and B will investigate the complete dose-response curve and the impact of lower doses on potential development of resistance. A dose-response curve will be fit to the data from Parts A & B using functional uniform priors.

9.4.1.3. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling and Simulation Department, GlaxoSmithKline. Plasma GSK2838232 concentration-time data will be analyzed by non-compartmental methods with WinNonlin Version 6.1 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:

Plasma GSK2838232 Pharmacokinetic Parameters to be Estimated:

Study Day	Parameters
1	AUC(0-24), Cmax, tmax, tlag, C24
10	AUC(0-τ), Cmax, tmax, t½, C0, Cτ, CL/F, R_AUC, R_Cmax, R_Cτ

Results based on samples collected from a subject with emesis within 4 hours of the dose will not be considered as evaluable.

All PK data will be stored in the R&D archives, GlaxoSmithKline.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline. Details of the statistical analyses will be provided in the RAP. An outline is provided below:

Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. Plasma GSK2838232 PK parameters, with the exception of tmax and tlag, will be log-transformed prior to analysis.

Dose proportionality of plasma GSK2838232 PK parameters from Day 1 [AUC(0-24) and Cmax] and Day 10 [AUC(0-τ) and Cmax] will be assessed using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI. The accumulation ratio (R) and steady-state assessments will be performed, if quality of the data permits. Comparisons of Day 10 with Day 1 PK for each dose will be used for the accumulation ratio (R) evaluation. Pre-dose concentrations between Days 7-10 will be used for steady-state assessment.

9.4.2. Secondary Analyses

9.4.2.1. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between various PK parameters (e.g., AUC, Cmax, Cτ, etc.) and PD measures (e.g., log10 reduction from baseline in plasma HIV-1 RNA on Day 11 or safety

parameters) will be explored using various models including Emax. The relationship between dose and PD measures will also be explored. Details of the PK/PD exploratory analyses will be provided in the RAP.

9.4.2.2. Viral Genotyping and Phenotyping Analyses

Viral genotypic/phenotypic data will be listed and descriptive summaries will be provided. Details of the analyses will be provided in the clinical virology report.

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 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 or designee 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 or designee 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.

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.

10.8. Review Committees

The Safety Review Team (SRT) is a GSK cross-functional team reviewing all available safety data related to the project, including in-stream data from this study, in an ongoing manner. The SRT is an internal GSK requirement put in place to ensure holistic evaluation of the safety profile of an investigational product with systematic, periodic and documented reviews of available safety data, with the appropriate communication and escalation of new findings that have the potential to impact patient safety

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

µg/mL	Microgram per millilitre
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredient
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUC(0-24)	Area under the concentration-time curve from zero (pre-dose) to 24 h
AUC(0-48)	Area under the concentration-time curve from zero (pre-dose) to 48 h
AUC(0-t)	Area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration
BCRP	Breast cancer resistance protein
BID	Twice daily
Bpm	beats per minute
BVM	Bevirimat
BIL	Bilirubin
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
C24	24 hour trough concentration
CDC	Center for Disease Control and Prevention
CI	Confidence interval
CL/F	Oral Clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CPK	Creatine Phosphokinase
CRF	Case report form
cTnI	Cardiac troponin I
CV	Coefficient of variation
CVb	Between-subject variability
CYP	Cytochrome P450
DDI	Drug Drug Interaction
DNA	Deoxyribonucleic acid
EC50	50% protection against resistant mutant HIV infection

ECG	Electrocardiogram
FC	Fold Changes
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FTIH	First time in Human Study
g	Gram
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour(s)
HBsAg	Hepatitis B surface antigen
hcG	Human chorionic gonadotrophin
HDPE	High density polyethylene
hERG	Human Ether-a-gogo Related Gene
HIV	Human Immunodeficiency Virus
IC50/90	50% or 90% maximal inhibitory concentration
IEC	International Ethics Committee
IQ	Inhibitory quotient
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous
IVRS	Interactive voice response system
kg	Kilogram
L	Litre
LLOD	Lower limit of detection
MC	Melanocortin
MedDRA	Medical Dictionary for Regulatory Activities
mg/mL	Milligram per millilitre
MI	Maturation inhibitor
mL	Milliliter
mRNA	messenger Ribonucleic Acid
ND	Not done
ng/mL	Nanogram per millilitre
nm	Nanometer
NO	Not observed
NOAEL	No Observed Adverse Effect Level
NTproBNP	N-terminal prohormone of brain natriuretic peptide
NSVT	Non-sustained ventricular tachycardia
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBL	Peripheral Blood Lymphocytes
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamics
PPD	Pharmaceutical Product Development
P-gp	P-glycoprotein
PHIV	Pseudo- HIV

PiB	Powder-in-bottle
PK	Pharmacokinetic
PoC	Proof of Concept
PI	Protease Inhibitor
QD	Once daily
RAP	Reporting and analysis plan
RIBA	Recombinant Immuno-Blot Assay
RT	Reverse Transcriptase
SAE	Serious adverse event
SDD	Spray Dried Dispersion
SRM	Study reference manual
t½	Terminal elimination half-life
TEM	Transmission Electron Microscopy
tlag	Time of first quantifiable concentration
tmax	Time of occurrence of Cmax
U	Units
UGT	Uridine 5'-diphospho-glucuronosyltransferase
Vz/F	Mean apparent oral volume of distribution
WPW	Wolff-Parkinson-White

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Abbot, Roche HIV kit
Chiron RIBA
Inform
Monogram
Phoenix WinNonlin
SAS
Tybost (cobicistat)

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

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

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin1, 2	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic3	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained within 24hrs after last dose[5] • 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

for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high-performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week • 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. 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.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

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

12.4. Appendix 4: Genetic Research

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK2838232/RTV 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 or 2 ml saliva sample will be taken for Deoxyribonucleic acid (DNA) extraction. A 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/saliva 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/saliva 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/saliva 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.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT 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.

12.5.2. 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:
c. Results in death
d. 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.
e. 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.

f. 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

g. Is a congenital anomaly/birth defect

h. 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

i. 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.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Definition of Cardiovascular Events

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

12.5.4. 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. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by

the scale's developer.

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.5.5. 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.

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.
- By specific request, the investigator is obligated to report any grade 2 or higher "alteration in personality-behavior or in mood" or "altered mental status" adverse events that occur in subjects taking this drug, to GSK within 3 days.
- 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.

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data

on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.

- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF

- Facsim0ile 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.

SAE reporting to GSK via PIMS

- Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the Medical Monitor or protocol contact:
  - SAE listing
  - Demographic listing
  - Study treatment listing
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
- If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the Medical Monitor or protocol contact. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.6. Appendix 6: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24hrs 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 discontinue study medication and be withdrawn from the study
- This will only be included if either of the following apply:
- 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 report the event and submit it to GSK within 24hrs 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.

12.7. Appendix 7: Country Specific Requirements

No country-specific requirements exist.

12.8. Appendix 8: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events Version 1.0, December 2004; Clarification August 2009

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
DERMATOLOGIC				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE AND METABOLIC				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia **Report only one and specify location**	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< *30 years of age*	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] ≥ *30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< *30 years of age*	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
NEUROLOGIC				
Acute Central nervous system (CNS) Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay < *18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures *New Onset Seizure* ≥ *18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< *18 years of age* *(includes new or pre-existing febrile seizures)*	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
PREGNANCY, PUERPERIUM, AND PERINATAL				
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	World Health Organization (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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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 < Lower limit of normal (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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 Estimated glomerular filtration rate (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*
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Low Density Lipoprotein (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*
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY				
Absolute cluster of differentiation 4 (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

1. Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
2. As per Bazett's formula.
3. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
4. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.
6. Bone mineral density (BMD) t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.
7. Definition: A delivery of a live-born neonate occurring at ≥20 to <37 weeks gestational age.
8. Definition: A clinically recognized pregnancy occurring at <20 weeks gestational age.
9. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
11. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12. WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.
13. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
14. Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as Grade 2, if <10% of the total bilirubin.
15. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
16. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
17. Male and female sexes are defined as sex at birth.
18. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

12.9. Appendix 9: 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:

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

7. peripheral blood smear
8. indirect bilirubin (abnormal if increased > 50% from baseline)
9. haptoglobin (abnormal if ≤ 25 mg/dL)
10. 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:

11. peripheral blood smear
12. indirect bilirubin
13. haptoglobin
14. 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 9.

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:

15. Temperature > 38.5°C
16. Lymphadenopathy
17. Pharyngitis
18. 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 10.5.

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:

19. Temperature > 38.5°C
20. Lymphadenopathy
21. Pharyngitis
22. 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 10.5.

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 10.5.

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 24 hours via phone or fax. The subject should be closely followed everyday until resolution of the reaction. The subject should remain on the study to be followed for safety and PK as outlined in Section 10.5.

ALLERGIC REACTION

Grade 1 allergic reaction (Pruritis 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:

23. Temperature > 38.5°C
24. Eosinophilia
25. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
26. 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.

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:

27. Temperature > 38.5°C
28. Eosinophilia
29. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
30. 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.

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

12.10. Appendix 10: Protocol Amendment Changes

Protocol Amendment 1 (26-Apr-2017) from the original protocol (09-Nov-2016)

Where the Amendment Applies

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

List of Specific Changes: (**bold** indicates text added and ~~strikethrough~~ indicates text removed)

Summary of Protocol Amendment Changes with Rationale

Amendment 1 includes minor updates to Inclusion criteria (IE) criteria, including clarification on use of pre- or post-exposure prophylaxis, and removal of exclusionary requirements related to concomitant medications and tobacco and alcohol use during the study. Guidance around relevant habits is included in the Lifestyle section of the protocol and adjustments were made to reduce restrictions on these requirements. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirements. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Furthermore, the serial ECG collection (up to 6h post-dose) was removed on Day 5. Finally, the post-study care guidance was updated to include an option for subjects to receive reimbursement for marketed ART for a limited period after completion of study treatment and follow up. Minor clarifications, reformatting of tables, re-numbering of sections and correction of typographical errors were also made throughout this amendment.

List of Authors

Rationale for change

The list of authors was updated based on internal GSK team personnel changes.

Revised Text

PPD	PTS, Ware, UK
	GCSP, Stockley Park, UK
	Infectious Diseases, Clinical, Upper Providence, PA, US
	Clinical Statistics, GSK, Upper Providence, PA, US
	HIV DPU, RTP, NC, US
	Virology, HIV DPU, RTP, NC, US
	CPMS, GSK, RTP, NC, US

PPD

HIV DPU, RTP, NC, US

Clinical Pharmacology, ViiV Healthcare, RTP, NC, US

PCPS, GSK, Upper Providence, PA, US

PCPS, GSK, Collegeville, PA, US

~~Clinical Statistics, PAREXEL, RTP, NC, US~~

~~Infectious Diseases, Clinical, Cambridge, MA, US~~

Medical Monitor/SAE Contact Information

Rationale for change

The sponsor and medical monitoring information was updated to reflect the current contact information for safety and medical monitoring.

Revised Text

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor/**SAE contact information**	PPD ~~MD~~ **Pharmaceutical Product Development (PPD) Safety Hotline**	PPD			~~Boston, MA~~**PPD, 929 North Front Street, Wilmington, NC 28401**
Secondary Medical Monitor	PPD MD				GlaxoSmithKline 1250 St Collegeville Rd Collegeville, PA 19426
~~SAE contact information~~	PPD ~~MD~~				~~Boston, MA~~

Synopsis: Design, Treatment Arms and Duration

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced. As synopsis being a standalone document, cross-referenced has been removed.

Revised Text

Fourth paragraph

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from ~~ongoing~~ Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) ~~is being~~ **was** assessed.

Sixth paragraph

HIV Drug Resistance: Following cessation of GSK2838232/cobi dosing for 10 days, there will be prolonged exposure to waning plasma concentrations of GSK2838232, because of the long t½ (i.e., in the "tail" of the PK profile). However, based on in vitro resistance passage data with GSK2838232 [and unlike with many other ARV therapies], there appears to be a limited likelihood of developing maturation resistance mutations in HIV-infected subjects due to its virologic ~~profile [GSK Document Number 2013N163221_00]~~.

Section 2 Introduction

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

GSK2838232 is a novel **human immunodeficiency virus (**HIV**)**-1 maturation inhibitor (MI) that is being developed for the treatment of HIV-1 infection in combination with other antiretrovirals (ART).

Section 2.1 Study Rationale

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

This 'proof of concept (PoC)' open-label study is being conducted to characterize the acute antiviral activity, pharmacokinetics (PK), the relationship between PK and antiviral activity, and safety of GSK2838232 given with 150 mg **once daily (**QD**)** cobicistat (GSK283232/cobi), administered across a range of doses over 10 days in HIV-1 infected patients. A two part adaptive and dose ranging design is to be applied in this study. Data from this study will be utilized to select doses for further studies in Phase IIb.

Section 2.2 Brief Background

Rationale for change

Abbreviation used on first instance has been defined.

Addition of abbreviation for AIDS in first paragraph

Combination antiviral therapy with inhibitors of HIV protease, integrase, entry and reverse transcriptase (RT) has demonstrated significant improvement in **acquired immunodeficiency syndrome** (AIDS)-related morbidity and mortality over the last 10-15 years.

Addition of abbreviation for RNA in second paragraph

Prior validation of this target was demonstrated with the HIV maturation inhibitor known as bevirimat (BVM; [Martin, 2007a; Martin, 2007b; Martin, 2008; NORVIR, 2013]). BVM reached Phase II studies in HIV patients; however, only modest reductions in plasma HIV-1 ribonucleic acid (RNA) concentrations were observed in Phase IIa monotherapy studies [Mahmood, 2006; Martin, 2007] and a pattern of polymorphic (differential) antiviral activity [Wainburg, 2010] led to termination of BVM development. The average decrease from baseline to Day 14 plasma HIV-1 **ribonucleic acid** (RNA) was 0.54 and 0.70 log10 copies/mL for 200 mg and 300 mg twice daily regimens (Table 2); all subjects achieved plasma BVM concentrations above the in vitro EC90. Responders, classified based on 5 polymorphisms in HIV-1 gag (at positions 369, 370, and 371), achieved an average 1.15 log10 copies/mL reduction in plasma HIV-1 RNA, while an average 0.17 log10 copies/mL reduction was achieved for non-responders.

Section 2.2.2 Clinical Summary of Safety and Pharmacokinetics

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Revised Text

To date, GSK2838232 has been evaluated in three completed clinical studies with or without **ritonavir** (RTV) (GSK2838232/r). A fourth study (204953) ~~is on-going as of 1st November~~ **completed late** 2016 **and data analysis is ongoing**. Full details of the clinical results can be found in the Investigator's Brochure.

Section 2.2.2.1 Clinical Summary of Safety

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Revised Text

~~Fifty~~ **As of November 2016 fifty**-three subjects ~~have~~ **had** been exposed to GSK2838232 in 3 completed studies. One study (204953) ~~is~~ **completed in late 2016 and the analysis of results are** ongoing (~~52 subjects have been~~ **63 subjects were** exposed to GSK2838232/r or placebo so far **in this study**). Overall, drug-related adverse events have been few and mild, and included headache, dizziness, fatigue, nausea, and palpitations and anxiety. Similarly, treatment-emergent laboratory abnormalities have also been few and mostly grade 1. There have been no discernible patterns, thus far, in terms of AEs or laboratory abnormalities.

Section 2.2.2.2 Study 204953 (completed); Pharmacokinetic Data

Rationale for change

Minor clarifications were made to this section to reflect current status of studies being referenced.

Change in Heading

Section 2.2.2.2 Study 204953 (~~on-going~~ **completed**); Pharmacokinetic Data

Section 4.4.1 Risk Assessment

Rationale for change

Abbreviation used on first instance has been defined.

Revised Text

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
HIV-1 Infection/Patient population		
HIV Resistance Propensity for co-meds and possible **Drug-Drug Interactions (**DDIs**)**	HIV Drug Resistance to unique mechanism Recognize HIV patients have a higher chance of comorbidities/diseases and a risk of taking a medicine or product contraindicated in the study	Closely monitor HIV viral load and genotypic resistance Strict adherence to protocol criteria around concurrent meds

Section 5.1 Inclusion Criteria

Rationale for change

Changes were made to this inclusion criteria to clarify that prior use of pre- or post-exposure prophylaxis would not exclude a subject from participation as long as last dose was 6 weeks before starting study treatment.

Revised Text

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY

5 . Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening. No current and no prior ART. **(A previous course of pre- or post-exposure prophylaxis is allowed provided that it was completed at least 6 weeks prior to the first dose of study drug).**

Section 5.2 Exclusion Criteria

Rationale for change

This exclusion criteria was removed and the guidance for use of concomitant medications was further addressed in Section 6.12, Concomitant Medications and Non-Drug Therapies. The Relevant Habits section of the Exclusionary criteria was also removed and addressed in Section 6.10, Lifestyle and/or Dietary Restrictions, with the exception of illicit drug use. Smoking and limited alcohol use are no longer exclusionary. Additional clarification added to note that positive Hepatitis C result would need to be confirmed by RIBA. Abbreviation used on first instance has been defined. Additional minor typographical errors were corrected.

Revised Text

~~CONCOMITANT MEDICATIONS~~
~~5. 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 GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.~~

RELEVANT HABITS
~~6. History of regular alcohol consumption within 6 months of the study defined as:~~ ~~• An average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.~~ ~~7. Smoking is an exclusion criteria for this study. Urinary cotinine levels indicative of~~

~~smoking at screening.~~ 6. Chronic marijuana or use of other elicit medications (cocaine, heroin) is an exclusion criteria.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

7 . Presence of hepatitis B surface antigen (HBsAg), positive **(confirmed by Recombinant Immuno-Blot Assay [RIBA])** hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.

19 . Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<45 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
*QTc interval	>450 msec	

*The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in ~~204953~~**200911** will be Fridericia's formula.

Section 6.1 Investigational Product and Other Study Treatment

Rationale for change

Minor typographical error corrected in this section.

Revised Text

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Method for individualizing dosage:	Capsules supplied in high-density polyethylene bottles for individualized dosing by the clinic	~~Capsules~~ **Tablets** supplied in bulk containers for individualized dosing by the clinic

Section 6.9 Treatment after the End of the Study

Rationale for change

Additional language was included in this section to allow subjects to opt to receive reimbursement from GSK for up to 3 months for marketed antiretroviral therapy (as

directed and prescribed by physician) based on the CDC guideline recommendations that patients be put on ARTs when diagnosed with HIV (test and treat guidelines).

Revised Text

~~Subjects will not receive any additional treatment from GSK.~~

Subjects receiving GSK2838232 may opt to receive marketed antiretrovirals after the completion of 10 days of GSK2838232 dosing and study follow-up visits (through Day 21) eligible for sponsor company reimbursement up to a maximum of 90 days. The selection of antiretrovirals will be investigator-chosen.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing ~~specific~~ **reimbursement for** post-study treatment.

Section 6.10.1 Meals and Dietary Restrictions

Previous section number 6.12

Rationale for change

This section was updated to remove language around meal provisions (language consistent for an in-patient trial). As this is an out-patient trial, it will be up to trial site to arrange when/how meals are provided during a subject's participation in the trial. The section 'Lifestyle and/or Dietary Restrictions' had no content described under it. The sections 'Meals and Dietary Restrictions' and 'Alcohol, Caffeine and Exercise' has been moved as sub-sections under the section 'Lifestyle and/or Dietary Restrictions', as the sub-sections are related to this section.

Revised Text

Second Bullet

Doses will be given in the fed state (light breakfast), following overnight fasting (>10 hours). ~~Lunch will provided ≥4 hours after the dose; water will be allowed ad libitum throughout.~~

Section 6.10.2 Alcohol, Caffeine and Exercise

Previous section number 6.13

Rationale for change

Adjustments were made to these lifestyle habits to eliminate restrictions on use of tobacco products, reduce restrictions on alcohol use and to allow occasional and light exercise during study treatment.

Revised Text

Alcohol, Caffeine~~, Tobacco~~ and Exercise

- ~~Subjects should refrain from alcohol for 48 hours before screening and then for 48 hours prior to admission and baseline assessments (on Day 1). Alcohol is then not permitted for the duration of the treatment period (through Day 10) and until the final follow-up visit.~~
- ~~Use of tobacco products is not allowed from screening until after the final follow-up visit~~
- ~~Subjects will~~ **During the study alcohol consumption should be limited to the following:**
  - **An average weekly intake of <14 drinks for males or <7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits.**
- Subjects ~~will~~ **should** abstain from strenuous exercise ~~for 72 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities~~ during ~~studies (e.g., watch television, read).~~**the treatment period.**

Section 6.11 Contraception

Rationale for change

This section was updated to clarify that use of oral contraceptives are permitted during the study.

Revised Text

Second paragraph

Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. ~~**There**~~ **Although use of oral contraceptives is permitted,** t~~T~~here is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.

Section 6.12 Concomitant Medications and Non-Drug Therapies

Previous section number 6.14

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous section 6.12) and 'Alcohol, Caffeine and Exercise' (previous section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 6.10), the section has been re-numbered.

Deleted Text

- ~~Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 for each treatment period. A positive result will lead to exclusion from the remainder of the study.~~
- ~~The Principal Investigator must be informed as soon as possible about any medications taken from the time of screening until the subject is discharged from the study. Over-the-counter medications will not be permitted during the treatment period except as needed to treat an AE. If medication is needed, use should be restricted to 4 hours after dosing if possible.~~

Section 6.12.1 Permitted Medications and Non-Drug Therapies

Previous section number 6.14.1

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous section 6.12) and 'Alcohol, Caffeine and Exercise' (previous section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 10), the section has been re-numbered.

Revised Text

Addition of Second bullet

- **Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study. Subjects must notify their Investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential for interactions between such treatments and the study medications.**

Section 6.12.2 Prohibited Medications and Non-Drug Therapies

Rationale for change

Adjustments were made to the concomitant medication section to clarify that certain (medically necessary) medications were allowed and that all medication use should be discussed with the investigator. As section on 'Meals and Dietary Restrictions' (previous section 6.12) and 'Alcohol, Caffeine and Exercise' (previous section 6.13) has been moved under Lifestyle and/or Dietary Restrictions' (Section 10), the section has been re-numbered.

Previous section number 6.14.2

Revised Text

- ~~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.~~
- **Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 and at additional timepoints throughout the study. A positive result will lead to exclusion from the remainder of the study.**

Section 7.1 Time and Events Table

Rationale for change

The Time and Events table was updated to remove the post-dose 12-lead ECG on Day 5, which remains in line with the FDA's guidance regarding days on which to perform post-dose (2 & 6 hours to capture near Tmax) ECGs. Modifications were also made to the pharmacokinetics sampling, allowing for the 12 h PK collection timepoint on Day 1 and 10 to be optional. Visit/procedure windows were included to allow more flexibility with scheduling of assessments. Also minor clarifications were made and typographical errors were corrected.

Revised Text

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Informed Consent	X																
Review inclusion/exclusion	X		X														
Demography including height, weight and BMI	X																
Brief physical			X														
Medical/medication/ drug/alcohol history	X		X														
CDC Classification	X		X													X	X
Prior antiretroviral therapy	X																
12-lead ECG[3]	X		X			X	~~X~~			X		X	**X**	X		X	X
Holter (24 hr)	X																
Vital signs[4]	X		X			X	X			X		X		X		X	X
Drug screen	X		X			X						X				X	
Hepatitis B Surface antigen and hepatitis C antibody testing	X																
Serum or urine β-hCG (WoCBP only)	X		X														X
Clinical lab tests (inc troponin)	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Fasting lipid panel	X																X
AE assessment[5]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Con Medication Review	X		X	X	X	X	X			X	X	X	X	X	X	X	X
HIV-1 RNA PCR[6]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Lymphocyte subsets[7]	X		X										X				
Plasma for genotype/phenotype[8]			X			X	X			X			X			X	X
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		~~X~~**X**[14]
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														
~~**AE enquiry**~~[13]			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Telephone call to IVRS[13][14]	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Plasma for storage[15]			**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

1. Screening will occur within **14-**30 days prior to the first dose of study drug.
2. Table is set up for the weekend during dosing to occur on Days 6 and 7. If the weekend occurs on Days 5 and 6, perform all "Day 5" assessments on Day 7.
3. On Day 1, ECGs ~~(x2)~~ will be performed pre-dose , and then 1, 1.5, 2, 3, 4 and 6 hours post dose. The ~~pre-dose~~ ECGs should be performed at least 5 minutes apart and preferably within 1 hour prior to dose. On Days 4~~, 5~~ and 8, ECGs will be obtained prior to morning dosing and at 2, 4 and 6 hours post-dose. **To accommodate scheduling, serial ECGs collected on Days 4 and 8 may be performed ± 1 day.** On Day 10, ECGs ~~(x2)~~ will be performed pre-dose, and then 1, 1.5, 2, 3, 4 and 6 hours post dose. On Day 11, an ECG will be obtained prior to the 24-hour PK sample. **ECGs will be performed in triplicate at all timepoints.**
4. BP, RR, HR and temperature will be obtained at Screening (x1) and Day 1 pre-dose (x2). BP and HR will be obtained on Day 1 at 2 hours post-morning dose and on Days 4, 5 and 8 pre-dose. BP and HR will be obtained on Day 10 at pre-dose and 2 hours post-morning dose, and at **day 12 and** Follow-up **(Day 21)**.
5. Only SAEs related to study participation will be collected between screening and Day 1. **An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status.**
6. On Days 1-5 and 8-10 samples for HIV-1 RNA PCR collected before morning dose. On Days 1, 10 and 11 two samples for HIV-1 RNA PCR will be collected 5-30 minutes apart. **HIV-1 RNA PCR samples will also be collected on days 12, 14 & Follow-up (Day 21).**
7. Lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+and CD8+counts).
8. Blood samples for phenotype and genotype will be collected at pre-dose on Days 1, 4, 5 and 8 in the morning on Day 11 and at follow-up.
9. Serial plasma samples (2 mL) for determination of GSK2838232 will be collected on Day 1 and Day 10 at pre dose (within 15 minutes prior to dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 **(optional),** and 24 hours **(to occur on morning of Day 2** post-am dose and **in the morning on Day 11)** . Pre-dose PK samples (within 15 minutes prior to dose) will be taken on the mornings of Days 3, 4, 5, 8 and 9 and a single sample will be taken on Days 12 and 14.
10. Samples (2 x 0.5mL) of plasma for assessment of immunological markers at screen, baseline (pre-dose) and day 11
11. Subjects will receive a single dose of GSK2838232 and cobicistat each morning with a light breakfast meal and 240 mL of water from Day 1 to Day 10. Doses taken in the clinic will be administered after an overnight fast of at least 10 hours .On Days 6 and 7, doses will be self administered but confirmed by phone
12. PGx sample should be collected on Day 1.

~~13. An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status~~

13. A screening/registration call should be made to the IVRS to register the subject at screening. An additional call will be made to document a screen failure. A randomization call should be made to the IVRS system approximately one week prior to scheduled Day 1. Note: The randomization call must be made in order to have study drug on site for Day 1. Additional calls will be made every day that the subject has a scheduled study visit to the clinic. If a subject terminates the study prematurely a call should be made to the IVRS
14. Only if early termination visits occur during the treatment period.
15. **Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally these samples will be used when needed, such as when samples are lost or arrive at the laboratory unevaluable.**

AE = Adverse event; CDC= Center for Disease Control and Prevention; ECG = Electrocardiogram; ET = Early termination; hCG = Human chorionic gonadotrophin; HIV = Human immunodeficiency virus; IVRS= Interactive Voice Response System; PCR = Polymerase chain reaction; PK=Pharmacokinetic.

Section 7.2 Visit Windows

Rationale for Addition

Visit/procedure windows were included to allow more flexibility with scheduling of assessments.

New Section

Screening (baseline to pre-dose): All screening assessments should take place within 14-21 days prior to the first dose. The screening visit window may be extended to 30 days upon discussion with the Medical Monitor (i.e.; subject has scheduling conflicts or any screening assessment needs to be repeated).

Days 4 and 8: Based on subject and clinic schedule, Day 4 and Day 8 serial (up to 6h post-dose) ECG assessments may be conducted ± 1 day.

Weekend(s): The T&E table is set up for study start (Day 1) to occur on a Monday and Days 6 and 7 to fall on the weekend. If the weekend occurs instead on Days 5 and 6, Day 5 assessments should be performed on Day 7. The study start (Day 1) may also be adjusted to allow visits with assessments to be conducted over the weekend based on subject and clinic schedule.

Assessments: The following applies to timing of procedures:

- **Window for assessments ≤ 4 h post-dose = ± 5 minutes**
- **Window for assessments >4 and <u>< 12 h post-dose = ± 15 minutes</u>**
- **Window for assessments ><u>12 h post-dose = ± 30 minutes</u>**

End of Treatment visit: should be within 14 days from last dose of study drug. If a subject is unable to return to the clinic for any reason site staff are encouraged to telephone the subject for assessment of adverse events.

Section 7.3.1 Holter Monitoring (Screening criteria)

After addition of new section before this section, the section numbers from this section until Sections under 7.0 are re-numbered using the next available section number.

Rationale for Change

Minor alterations were made regarding the order of screening procedures, including the Holter monitoring requirement to allow flexibility based on clinic and subject schedule.

Revised Text

The 24-hour Holter monitoring ~~should only~~ **will** be performed ~~at~~ **during the** Screening ~~after the subject has met all other inclusion criteria.~~ **period using a Holter monitoring device supplied by the Sponsor.**

Analysis of the Holter tapes will consider the following:

- Heart rate (brady**cardia** and tachycardia)

- Normal and aberrant beats
- Number of supraventricular contractions, premature atrial contractions, premature ventricular contractions, couplets, triplets, and ventricular tachycardias
- Atrio-ventricular conduction defects
- Atrial fibrillation and flutter

Section 7.5.1.1 Time period and Frequency for collecting AE and SAE information

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

Bullet 4

- All SAEs will be recorded and reported to ~~GSK~~ **Sponsor** within 24 hours, as indicated in Appendix 5, Section 12.5.

Section 9.3.2 Interim Analysis

Rationale for Change

Minor corrections and clarifications were made to this section.

Revised Text

An interim analysis of preliminary safety, tolerability, PK and antiviral activity will occur after subjects of Part A Cohort 1 complete their Day 13 visit. If ~~based on this review~~ the Cohort 1 dose is determined to be the highest dose **based on this review** (e.g**.,** the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects), the Bayesian posterior probability that the log10 viral load decline from baseline is greater than a cut-point will be calculated. If the Bayesian probability from Cohort 1 is less than 70%**,** this will provide ~~evidenceto~~ **evidence to** not move forward into Part B. Otherwise, the study team will review the data in order to make a dose selection decision for the subsequent Part B Cohorts. If the pharmacokinetic exposures after the 100 mg GSK2838232/cobi dose look similar to those obtained with 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) **GSK2838232** doses.

Maximum change and change from baseline in plasma HIV-1 RNA will be summarized by treatment or by assessment day. The proportion of subjects with plasma HIV-1 RNA <400 and <50 copies/mL will be summarized by treatment and assessment day. The analyses will be done for both PP and ITT exposed population if **the** two populations are not the same.

Section 10.3 Quality Control (Study Monitoring)

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

First Bullet

In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors **or designee** 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.

Section 10.5 Study and Site Closure

Rationale for Change

Minor clarifications made regarding Sponsor (to include PPD).

Revised Text

First Bullet

Upon completion or premature discontinuation of the study, the GSK monitor **or designee** 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.

Section 11 References

Rationale for Change

Have mentioned the references as per GSK style guide and template.

Revised Text

Elion R, Cohen C, Gathe J, Shalit P, Hawkins T, Liu HC, **et al**. ~~Mathias AA, Chuck SL, Kearney BP, Warren DR.~~ Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine.tenofovir df in the initial treatment of HIV infection. *AIDS*. 2011; 25:1881-1886.

Gallant JE, Koenig E, Andrade-Villaneuva J, Chetchotisakd P, deJesus E, Antunes F, Arastéh K, **et al**. ~~Moyle G, Rizzardini G, Fehr J, Liu Y, Zhong L, Callebaut C, Scwarcberg J, Rhee MS, Cheng AK.~~ Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV type 1-infected patients: week 48 results. *J. Infect. Dis.* 2013; 208-:32-39.

Kakuda TN, Opsomer M, Timmers M, Iterbeke K, Van De Casteele T, Hillewaert V, **et al.** ~~Petrovic R, Hoetelmans RMW.~~ Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. *J. Clin. Pharmacol.* 2009; 54:949-957.

Lalezari J, McCallister S, Gigliotti M, Cohen C, Elion R, **Brinson C,** et al. Safety and efficacy study of bevirimat (BVM) in heavily treatment experienced HIV+ patients identifies the target phase 3 study profile. ICAAC. 2008; Abstract: H891.

Martin DE, Blum R, Wilton J, Doto J, Galbraith H, **Burgess GL**, et al. Safety and pharmacokinetics of bevirimat (PA-457), a novel inhibitor of human immunodeficiency

virus maturation, in healthy volunteers. *Antimicrobial Agents and Chemotherapy*. 2007(b);Sep:3063-6.

Appendix 1 Abbreviations

Rationale for Change

The abbreviations used in the document are added to the list of abbreviations.

AIDS	~~Auto~~ Acquired immunodeficiency syndrome
BID	**Twice daily**
DDI	**Drug-Drug Interaction**
PPD	**Pharmaceutical Product Development**
QD	**Once daily**
RIBA	**Recombinant Immuno-Blot Assay**
~~t1/2~~**t½**	Terminal elimination half-life

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A Phase 2a, Multicenter, Randomized, Adaptive, Open-label, Dose Ranging Study to Evaluate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Cobicistat-boosted GSK2838232 Monotherapy Over 10 Days in HIV-1 Infected Treatment-Naive Adults

Compound Number: GSK2838232

Development Phase IIA

Effective Date: 09-NOV-2016

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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
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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): 116,094

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- 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 Signature	Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 200911

Rationale

GSK2838232 is a novel human immunodeficiency virus (HIV-1) maturation inhibitor that is being developed for the treatment of HIV-1 in combination with other antiretrovirals.

Three clinical studies of GSK2838232 (n=53 healthy subjects) have been completed thus far. One study (Study 204953) is on-going. Healthy subjects have received GSK2838232 or placebo in single or repeated dose designs, to a maximum single dose of 250 mg or repeated dose (for 11 days) of 200 mg QD, in combination with ritonavir (RTV).

Study HMI116787 (completed November 2013) was the First Time in Human study of GSK2838232 and assessed safety and tolerability of escalating doses (5 mg to 100 mg), food effect, and the impact of steady-state ritonavir on GSK2838232 pharmacokinetics (PK). Following successful completion of 3-month toxicology studies in rat and dog in 2014, clinical studies 200912 and 200207 were initiated. These were double-blind, placebo-controlled, single (Study 200912) and repeat-dose (Study 200207) escalation studies to investigate the safety, tolerability, and PK of GSK2838232 alone and when co-administered with ritonavir 100 mg once daily (QD) for 8-11 days. Further assessment of an alternative formulation was also an objective in Study 200912.

Both studies were prematurely terminated/completed in March/April 2015 because of concerns over cardiovascular (CV) toxicity, in particular a clinical CV serious adverse event (SAE) whereby the Food and Drug Administrating (FDA) imposed a clinical hold. Following submission of long-term (6-month rat, 9-month dog) chronic toxicology data and follow up to the clinical SAE in November 2015, the hold was released in January 2016 and Study 204953 was initiated.

Study 204953 is an on-going study and continues the single and repeat-dose exploration of safety and PK of GSK2838232 as well as the suitability of a new, capsule formulation. Doses of up to 250 mg GSK2838232/100 mg RTV (as single doses) or 200 mg GSK2838232/100 mg RTV (QD for 11 days) were studied. As of 26 October 2016, the study is ongoing with a cohort of subjects due to receive unboosted GSK2838232 (200mg BID) for 11 days.

These studies have shown GSK2838232 with or without RTV to be well tolerated and, together with daily RTV dosing (“boosting”), demonstrate a PK profile suitable for progression to HIV patients in this Phase IIa proof of concept 10-day, monotherapy study design. However, potential concerns over protease resistance necessitate a change to a pharmacoenhancer without antiviral effects in this study of GSK2838232 monotherapy. Therefore, for Study 200911, cobicistat (Tybost,150 mg QD) will be substituted for RTV.

The objective of Study 200911 is to understand the safety, PK and HIV antiviral profile of GSK2838232/cobicistat (GSK2838232/cobi) when given to HIV-infected, treatment naive, otherwise healthy adults. Approximately 10 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology, and PK data analysis,

approximately 8 subjects will be enrolled in each of between two and four Cohorts in Part B, which will be a parallel group design.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate antiviral activity of GSK2838232/cobi in HIV-1 infected patients during 10 days of monotherapy.	• Change from baseline (Day 1) in plasma HIV-1 RNA
• To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days.	• Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments.
• To characterize the pharmacokinetics of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days.	• GSK2838232 PK parameters following dose administration, as follows: **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Secondary	
• To explore the relationship between GSK2838232 exposure and change in plasma HIV-1 RNA	• GSK2838232 PK parameters Day 10 AUC(0-τ), Cmax, Cτ with Day 11 HIV-1 RNA change from baseline
• To assess the immunologic effect of GSK2838232/cobi when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ cell count to Day 11
• To explore the relationship between GSK2838232 exposure and safety or immunologic parameters, if appropriate.	• GSK2838232 PK parameters on Day 10: AUC(0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count

Objectives	Endpoints
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.	• Emergence of drug resistance mutations, if appropriate
• To estimate GSK2838232 accumulation and to assess attainment of steady state following administration of GSK2838232/cobi for 10 days in HIV infected subjects.	• **Accumulation:** GSK2838232 PK accumulation ratios (R): Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively • **Steady State:** pre-morning dose concentrations (C0) on Days 2 through 11
• To examine dose proportionality of GSK2838232 pharmacokinetic parameters following GSK2838232/cobi dosing for 10 days in HIV infected subjects.	• Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax, and Cτ at different dose levels for the assessment of dose proportionality
Note: Other exploratory objectives and endpoints will be specified in the RAP	

Design, Treatment Arms and Duration

Approximately 34 HIV-1 infected treatment-naive subjects will be enrolled overall.

This study is a 10-day monotherapy, open-label, adaptive, dose ranging, repeat-dose study and will be conducted as two parts with an interim (go/no-go) analysis performed after Part A (Table 1). Part A, Cohort 1 will evaluate a safe and well-tolerated dose level of GSK2838232 that has been tested (with RTV) in prior Phase I studies and that targets a high inhibitory quotient (IQ) value. Following the completion of an interim analysis of those data and according to criteria defined later in the protocol, further cohorts of 8 subjects will then be studied in Part B in a parallel design in two or more cohorts (depending upon the data obtained in Part A).

The totality of this data will provide a full dose-response of GSK2838232 over a wide dose range to explore the safety and PK/pharmacodynamics (PD) relationship of GSK2838232 in HIV-1 infected subjects and facilitate choice of doses for Phase IIb studies.

Table 1 Study Design for 200911

	Part A: GSK2838232/cobi Once Daily x 10 days[1]		Part B: GSK2838232/cobi Once Daily x 10 days[1,2]		
Cohort	N	232 Dose (mg)	Cohort	N	232 Dose (mg)
1	10	100			
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B, which are planned to run in a parallel, randomized fashion. All doses will be given with 150 mg cobicistat.
2. Part B GSK2838232 doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobi co-dosing) may be added (the maximum dose in Part B would not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] was lower in HIV infected subjects than in healthy subjects at the same dose level).

The possibility that an additional, unboosted GSK2838232 monotherapy cohort will be assessed in Part B is dependent on analysis of the PK data from ongoing Study 204953 where unboosted GSK2838232 at a dose of 200 mg twice daily (BID) is being assessed.

Subjects in both parts will have a screening visit within 30 days prior to first dose and a follow-up visit 7-14 days after the last dose. Maximum duration of study participation will be approximately 6 weeks.

HIV Drug Resistance: Following cessation of GSK2838232/cobi dosing for 10 days, there will be prolonged exposure to waning plasma concentrations of GSK2838232, because of the long t½ (i.e., in the "tail" of the PK profile). However, based on in vitro resistance passage data with GSK2838232 [and unlike with many other ARV therapies], there appears to be a limited likelihood of developing maturation resistance mutations in HIV-infected subjects due to its virologic profile [GSK Document Number 2013N163221_00].

Analysis

The primary objectives of this study are to investigate the safety, tolerability, PK and antiviral activity of 10 days repeated doses of GSK2838232/cobi in HIV-1 infected otherwise healthy subjects. Descriptive summaries will be provided for safety, PK, and HIV viral load data.

2. INTRODUCTION

GSK2838232 is a novel HIV-1 maturation inhibitor (MI) that is being developed for the treatment of HIV-1 infection in combination with other antiretrovirals (ART).

2.1. Study Rationale

This 'proof of concept (PoC)' open-label study is being conducted to characterize the acute antiviral activity, pharmacokinetics (PK), the relationship between PK and antiviral activity, and safety of GSK2838232 given with 150 mg QD cobicistat (GSK283232/cobi), administered across a range of doses over 10 days in HIV-1 infected patients. A two part adaptive and dose ranging design is to be applied in this study. Data from this study will be utilized to select doses for further studies in Phase IIb.

2.2. Brief Background

Combination antiviral therapy with inhibitors of HIV protease, integrase, entry and reverse transcriptase (RT) has demonstrated significant improvement in AIDS-related morbidity and mortality over the last 10-15 years. Emerging multi-class drug resistant viral strains and long-term toxicities warrant development of new classes of antiretroviral therapies targeting various parts of the HIV-1 viral life cycle [Wainburg, 2010]. The inhibition of maturation of HIV-1 is a novel target for drug development, distinct from viral protease RT or integrase [Saxena, 2012; Qian, 2009]. HIV maturation is the final cleavage step of the capsidSp1 (transcription factor) polyprotein that generates the functional capsid p24 protein. This mechanism of action results in accumulation of the uncleaved p25 protein with subsequent improper assembly of the HIV core, resulting in a non-infectious virion. Gel-based mechanism of action studies suggest that compound GSK2838232 acts as a maturation inhibitor. Western Blot analysis shows inhibition of capsid-Sp1 cleavage and accumulation of p25 in the presence of GSK2838232.

Prior validation of this target was demonstrated with the HIV maturation inhibitor known as bevirimat (BVM; [Martin, 2007a; Martin, 2007b; Martin, 2008; NORVIR, 2013]). BVM reached Phase II studies in HIV patients; however, only modest reductions in plasma HIV-1 ribonucleic acid (RNA) concentrations were observed in Phase IIa monotherapy studies [Mahmood, 2006; Martin, 2007] and a pattern of polymorphic (differential) antiviral activity [Wainburg, 2010] led to termination of BVM development. The average decrease from baseline to Day 14 plasma HIV-1 RNA was 0.54 and 0.70 log10 copies/mL for 200 mg and 300 mg twice daily regimens (Table 2); all subjects achieved plasma BVM concentrations above the in vitro EC90. Responders, classified based on 5 polymorphisms in HIV-1 gag (at positions 369, 370, and 371), achieved an average 1.15 log10 copies/mL reduction in plasma HIV-1 RNA, while an average 0.17 log10 copies/mL reduction was achieved for non-responders.

Table 2 Summary of Bevirimat Antiviral Response and PK in a 14-day Monotherapy Study in HIV-infected Adults

BVM dosage regimen	Mean (SD) viral load change from baseline to Day 14	[2]IQ	Plasma BVM [1]Cmin (μg/mL)	Plasma BVM [1]Cmax (μg/mL)	Plasma BVM [1]AUC(0-τ) (μg.h/mL)
200 mg BID (N=14)	-0.54 (0.64)	1.70	46 (41, 51)	58 (53, 64)	632 (571, 699)
300 mg BID (N=18)	-0.70 (0.77)	2.67	72 (65, 80)	91 (84, 99)	973 (890, 1064)

1. Cmin, Cmax, and AUC reported as geometric mean (95% CI).
2. IQ=geometric mean Cmin/in vitro EC90; reported EC90=27 μg/mL; all subjects achieved IQ ≥1.

AUC(0-τ) = Area under the concentration-time curve over the dosing interval; BVM = Bevirimat; CI = Confidence interval; Cmax = Maximum plasma concentration; Cmin = Minimum plasma concentration; EC90 = 50% protection against resistant mutant HIV infection; IQ = Inhibitory quotient; SD = Standard deviation.

Early clinical data for BMS955176, a second generation maturation inhibitor, have been recently presented [Nowicka-Sans, 2015]. In a 10-day monotherapy trial in HIV-infected patients, plasma HIV-1 RNA was reduced at doses of between 40 mg and 120 mg QD. All doses were well tolerated. The maximum change, seen between 10 and 12 days after starting dosing, was about 1.5 log10, which is substantially better than the effect demonstrated with BVM and may indicate the maximum expected clinical effect of inhibiting this viral target.

Although BMS955176 is currently in Phase II studies in HIV-infected patients, there are no maturation inhibitors approved for the treatment of HIV infection. The uncertainties of early drug development and continuing need for novel ART, especially for heavily treated/experienced HIV-infected persons, support continued compound development. GSK2838232's low nanomolar in vitro potency against multiple HIV-1 gag polymorphisms and broader spectrum across multiple HIV-1 subtypes indicates it has utility in this setting.

2.2.1. Preclinical Summary

Nonclinical pharmacology

Virology

GSK2838232, in vitro, is an inhibitor of HIV maturation by preventing the cleavage of the HIV gag structural subunit p25 to p24. GSK2838232 is a potent antiviral agent with a mean 50% maximal inhibitory concentration (50% maximal inhibitory concentration [IC50]) value of 1.6 nM (range: 0.8 to 4.3 nM) when tested in a panel of 26 HIV-1 isolates with various polymorphic gag genotypes in peripheral blood mononuclear cells (PBMCs), suggesting that GSK2838232 can inhibit a broad spectrum of HIV isolates. In another PBMC assay, GSK2838232 showed potent antiviral activity in 59 of 60 isolates with IC50 values ranging from 0.22 to 5.1 nM. GSK2838232 also inhibited HIV-1 strains containing the consensus Sp1 QVT region or the V370A polymorphism in MT4 cells (IC50 = 0.73 to 0.81 nM).

In an MT2 cell-based assay utilizing recombinant viruses harboring gag and protease from subjects before and after a protease inhibitor (PI) based regimen, GSK2838232 inhibited 12 of 15 viruses with a mean IC50 value of 1.7 nM (range = 0.4 to 3 nM). The remaining 3 viruses were not inhibited by GSK2838232 up to the top concentrations tested at 400 nM. There was no correlation of PI sensitivity and susceptibility to GSK2838232. GSK2838232 resistance mutations were selected for by serial passage of virus in a SupT1 cell-based assay with increasing concentrations of GSK2838232. In the lab strain NL4-3 and gag/protease recombinant viruses, the resistance mutation A364V arose and resistance confirmed by site-directed mutagenesis. This resistance mutation maintains susceptibility to other classes of anti-retrovirals including PIs and non-nucleoside RT inhibitors.

GSK2838232 was tested in vitro in combination with two marketed PIs, atazanavir and darunavir. Using a dose-wise additivity model, GSK2838232A showed additive anti-viral activity with both PIs.

Secondary Pharmacology

In a secondary pharmacology study, GSK2838232 was tested against a panel of receptors, ion channels and transporters and demonstrated no significant effect (IC50 of ≤1 μM). It is important to note that the selectivity for antiviral activity of GSK2828232 compared to all tested off-target activities was >100-fold, and the potential for organ toxicity was characterized in the nonclinical toxicology studies (see below).

In safety pharmacology studies in male rats, there were no hemodynamic changes or neurobehavioral effects following single oral doses up to 300 mg/kg. A single oral dose of GSK2838232 at 30 mg/kg or 300 mg/kg produced reversible increases in respiratory tidal volume (32% and 36%, respectively) and derived minute volume (17% and 26%, respectively) at 6 hours after dosing. These doses did not produce any effect on respiratory rate, airway resistance or body temperature. There were no respiratory effects in rats given 5 mg/kg (mean maximum plasma concentration [C_{max}] 0.12 μg/mL; AUC_{0-24} 1.0 μg.h/mL based on Day 1 of the 4-week repeat dose study). These findings were not considered to suggest a safety concern in humans.

GSK2838232 at the maximum feasible concentration, limited by solubility, of 4.09 μM (3.31 μg/mL) caused no inhibition of human ether-a-gogo related gene (hERG) tail current in Human Embryonic Kidney 293 cells stably transfected with hERG cDNA, indicating a low probability for interaction at the hERG channel.

In conscious telemetered male dogs (n=4), a single oral dose of GSK2838232 at 60 mg/kg (C_{max} 0.59 μg/mL; AUC_{0-24} 8.7 μg.h/mL based on Day 1 exposure data from the 4-week oral repeat dose toxicity study) was associated with one episode of non-sustained ventricular tachycardia in one dog lasting ~1.2 seconds. There were no effects on arterial pressures, heart rate, or electrocardiogram (ECG) interval durations. An investigative safety pharmacology cardiovascular study was conducted in telemetered dogs given 60 mg/kg/day for 4 weeks with serial monitoring by echocardiography, cardiac biomarkers, qualitative and quantitative electrocardiology, microscopy, and transmission electron microscopy (TEM) of the heart.

There were no changes in echocardiography endpoints, ECG intervals, ECG waveforms, arterial pressures, heart rates, serum cTpnI, N-terminal prohormone of brain natriuretic peptide (NTproBNP), or in heart tissue as assessed by TEM. With routine microscopy, one treated dog had a single focus of degeneration/necrosis of the tunica media (moderate) in an extramural artery and another treated dog had localised, mixed-cell inflammation (mild) along the epicardium of the coronary groove. Both changes have been reported in normal beagles and were considered of uncertain relationship to treatment in the absence of changes in any other structural or functional cardiovascular endpoints. The 28-day exposures were similar to the previous 4-week toxicity study in dogs: the C_{max} range at 60 mg/kg/day in this investigative safety pharmacology study was 0.542 to 2.00 μg/mL and range of AUC_{0-24} was 6.04 to 35.7 μg.h/mL. In subsequent repeat-dose studies in dogs treated for up to 9 months with up to 70 mg/kg/day, no changes were evident in cardiac biomarkers (including cTpnI and NTproBNP), functional (including ECG waveform) or structural (including microscopic evaluation) cardiovascular endpoints at slightly higher exposures than those achieved than in previous studies. The end of the 9-month study, gender averaged C_{max} at 70 mg/kg/day was 1.95 μg/mL and AUC_{0-24} was 38.8 μg.h/mL. These studies support an absence of GSK2838232-related functional or structural effects on the heart in preclinical testing. The No Observed Adverse Effect Level (NOAEL) was established at 20 mg/kg/day (on the basis of mild hepatic findings) with an associated are under the curve at 24 hours (AUC24) of 16.2 μg.hr/mL and Cmax 0.847 μg/mL.

Pharmacokinetics and product metabolism in animals

The PK of GSK2838232 were investigated in the mouse, rat, and dog. The oral bioavailability of GSK2838232 was low to moderate (~6% to 40%) depending on the species and formulation. Plasma and blood clearance were low and the volume of distribution at steady state was high relative to total body water. The half-life of GSK2838232 was short in the mouse and rat, but moderate in the dog. Systemic exposure of GSK2838232 generally increased in a less than dose-proportional manner. In rats, there were no differences in systemic exposure between single and repeat-dose administration, or between males and females. In a 7-day study in dogs, systemic exposures were generally similar between males and females and after single and repeat dosing; however, in a 4-week study, systemic exposures were higher in females than in males in the high-dose group (60 mg/kg/day) and higher after repeat dosing than after a single dose. The distribution of radioactivity in male pigmented rats following a single oral administration of [^{14}C] GSK2838232 at a target dose level of 20 mg/kg showed radioactivity was rapidly absorbed and widely distributed throughout the body with all tissues, except the brain and spinal cord. There were no tissues that retained detectable levels of radioactivity at 28 days post dose. In a bile duct canulated rat study, 30% of the administered dose was excreted in the bile as an acylglucuronide. In the same study, unchanged drug and metabolites were eliminated primarily in the bile and feces, while a mean of <1% of the dose was eliminated in urine.

In vitro, GSK2838232 is highly protein bound (>99.9%) and has low passive permeability. In vivo evidence suggests active uptake of GSK2838232 by transporters in the rat liver.

After single oral doses of 5, 100, or 300 mg/kg, the average liver to plasma ratio was 51, 17, and 10, respectively. After 7 days of dosing at 30, 100, or 300 mg/kg/day, liver to blood ratios ranged from 10 to 16.

In the 13-week repeat dose studies in dogs given 35 mg/kg BID (70 mg/kg/day), heart tissue collected at necropsy had GSK2838232 concentrations 2.5 to 5-times higher than the 24-hour post-dose plasma concentrations, similar to the previous 4-week CV investigative findings. In the 13-week repeat dose studies in rats given 300 mg/kg/day, heart tissue collected at necropsy had GSK2838232 concentrations approximately 3 times higher than the 24-hour post-dose plasma concentrations, similar to the previous 7-day findings. Overall GSK2838232 did not appear to be highly concentrated in heart tissue after repeat dosing and suggests that accumulation upon chronic dosing is unlikely.

Routes of metabolism identified in liver microsomal incubations and rat, dog, and human hepatocytes were N-dealkylation, oxidation, oxidative deamination, and glucuronidation, alone or in combination, with no human-specific metabolites detected. N-dealkylated products and glucuronidation were observed in rat plasma and the bile. In general, in vitro metabolite profiles of the nonclinical species and human were qualitatively similar, such that all metabolites of [^{14}C] GSK2838232 observed in human hepatocyte incubations were observed in rat and/or dog. Minor to trace levels of potential aldehydes metabolites formed as a result of N-dealkylation and oxidative deamination were observed in rat, dog and humans.

GSK2838232 did not show evidence for glutathione adduct formation in rat or human liver microsomes. Data from pooled human liver microsomes along with recombinant cytochrome P450 (CYP) enzymes suggest that in vitro the oxidative metabolism of GSK2838232 was primarily mediated by CYP3A4. Preliminary in vitro investigations showed GSK2838232 did not inhibit CYP1A2, 2C9, 2C19, 2D6, 3A4 and was not a metabolism-dependent inhibitor of CYP3A4. No drug interaction risk was identified for co-administrated substrates of UGT1A1, 1A3, 1A6, 1A9, 2B7, and 2B15, OAT1, OAT3, OATP1B1, OATP1B3 or OCT2 at a clinical dose of 200 mg GSK2838232/ritonavir (predicted Cmax 0.32 μM). Extrapolation of the clinical risk (using FDA and EMA regulatory guidance) did indicate a risk for GSK2838232-mediated inhibition of UGT1A4 and of gut contributions of CYP3A4, P-gp, and BCRP at the same clinical exposure; however, the potential for clinically significant interactions via these mechanisms is predicted to be low (<2 fold change in AUC). GSK2838232 did show weak induction of CYP3A4 enzyme activity. However, based on the maximum predicted plasma concentrations and high protein binding, the potential for clinically significant drug interactions through CYP3A4 induction by GSK2838232 appears to be low.

The inclusion of cobicistat as a CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is unlikely to produce a significantly different profile of GSK2838232 ADME (and therefore systemic exposure); however, there have been no preclinical studies conducted with GSK2838232 and cobicistat to date.

Toxicology

GSK2838232 administered by oral gavage in repeat dose studies up to 6 months duration resulted in no adverse treatment-related effects in rats given up to 300 mg/kg/day QD.

In dogs given up to 70 mg/kg/day (35 mg/kg/day BID), adverse liver effects were noted at this dose in the 9-month repeat dose study. Though isolated, low grade changes in heart rate and cardiac troponin I (cTnI) had been noted in 4-week toxicity studies in rats and dogs; however, there were no treatment-related structural or functional cardiovascular changes in studies of 3 months and greater duration as assessed by echocardiography, ECG, microscopy, and cardiac biomarkers, indicating an absence of GSK2838232-related functional or structural effects on the heart in preclinical testing.

Only non-adverse treatment-related changes were noted in the definitive 6-month rat study, which included occasional salivation in animals given 300mg/kg/day and minimal clinical pathology changes without histologic correlates (transient clinical chemistry changes at ≥5 mg/kg/day and reversible urine chemistry changes at 300 mg/kg/day). The NOAEL in this study was considered to be 300 mg/kg/day (mean AUC[0-t] 21.3 μg.h/mL, mean Cmax 1.77 μg/mL [Week 26 values for males and females combined]).

As noted above, dogs given GSK2838232 at 70 mg/kg/day for 9 months had minimal to moderate pigmentation (consistent with bile) with minimal to mild mixed cell infiltration in the liver and isolated mild increases in alanine aminotransferase (ALT) activity. These findings were considered adverse, but were reversible after the 6-week off-dose period. The NOAEL for this dog study was considered to be the mid-dose level of 20 mg/kg/day (mean AUC[0-t] 16.2 μg.h/mL, mean Cmax 0.847 μg/mL [Week 39 values for males and females combined]).

Data from genotoxicity assessments suggest that GSK2838232 does not present a genotoxic hazard to humans.

During discussions with the FDA regarding the resolution of the clinical hold, the Agency recommended that the sporadic cardiovascular changes observed in the early (1-month) rat GLP study at the highest dose level (300 mg/kg/day) should be considered when defining the NOAEL and establishing a safe dose of GlaxoSmithKline (GSK) for the initiation of this study protocol. Accordingly, for the initial PK studies, the reference dose level of 30 mg/kg/day in the 1-month rat study was initially used to define the NOAEL and therefore the values for fold cover at maximum projected mean exposure and Cmax in human subjects were lower, at >2.5-fold. However, based on the cumulative clinical safety data through Cohort 5 of Study 204953, the designated NOAEL for the most sensitive species (i.e., 20 mg/kg/day in the 9-month dog study based on liver endpoints) is currently used for assessing fold-cover for projected clinical dosing in this study**.**

The inclusion of cobicistat as a CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is unlikely to produce a significantly different profile of GSK2838232 ADME (and therefore systemic exposure and toxicity); however, there have been no preclinical studies conducted with GSK2838232 and cobicistat to date.

Full details of non-clinical and clinical data may be found in the current Investigator's Brochure (IB) [GSK Document Number 2012N151889_03].

2.2.2. Clinical Summary of Safety and Pharmacokinetics

To date, GSK2838232 has been evaluated in three completed clinical studies with or without RTV (GSK2838232/r). A fourth study (204953) is on-going as of 1st November 2016. Full details of the clinical results can be found in the Investigator's Brochure.

2.2.2.1. Clinical Summary of Safety

Fifty-three subjects have been exposed to GSK2838232 in 3 completed studies. One study (204953) is ongoing (52 subjects have been exposed to GSK2838232/r or placebo so far). Overall, drug-related adverse events have been few and mild, and included headache, dizziness, fatigue, nausea, and palpitations and anxiety. Similarly, treatment-emergent laboratory abnormalities have also been few and mostly grade 1. There have been no discernible patterns, thus far, in terms of AEs or laboratory abnormalities.

One subject in study 200912 discontinued treatment with RTV due to an AE. A 47-year-old female who developed right upper quadrant abdominal pain, nausea and flatulence associated with grade 4 elevations in ALT and aspartate aminotransferase, and grade 2 elevations in total bilirubin (BIL). She was diagnosed with a common bile duct obstruction due to gallstones that spontaneously resolved. The Investigator assessed this AE as unrelated to study treatment.

Due to sporadic CV-related safety signals in the early animal studies (see Section 2.2.2), intense CV monitoring was in place for all four studies.

One AE occurred in HMI116787 that was initially considered a CV AE but after further evaluation was considered not to be of cardiac etiology. Two CV AEs occurred in 200207 that were initially considered possibly related to GSK2838232 exposure. However, further evaluation confirmed that there is a low likelihood that these events were due to GSK2838232 exposure. A summary of each event is provided in the IB.

In ongoing Study 204953, there have been a small number of CV-related events of any sort: There have been no serious adverse drug reactions, and no clinically significant drug-related abnormal findings for 12-lead ECGs, vital signs, safety laboratory results (including cardiac troponin I), or telemetry. The following cardiovascular AEs were observed during the course of the study but were not considered to be caused by GSK2838232 exposure:

- In Part 1A (Cohort 1), Period 2, a subject was withdrawn due to an AE (low hemoglobin) prior to GSK2838232 exposure Day -2. A replacement subject was brought in, but was not dosed with GSK2838232 or placebo because during the 2-day RTV run-in, on Day -1, the replacement subject met the stopping criteria for telemetry due to as brief occurrence of asymptomatic, NSVT prior to the first dose of GSK2838232 or placebo. Because the subject was excluded from the study prior to the first dose of investigational drug, the NSVT was not considered to be a serious and unexpected adverse drug reaction that would qualify for IND safety reporting.

- In Part 1A (Cohort 1), Period 3 (Period "3A" for the purpose of differentiating between 100 mg GSK2838232/r vs. 200 mg GSK2838232/r), one subject was discontinued prior to the first dose of study drug due to a series of cardiovascular findings (pre-ventricular contractions on telemetry). None of the findings were abnormal or atypical, but the investigator determined that this would not be a good etiology to have in a subject about to receive investigational drug. Because the event occurred prior to first dose of investigational drug, the finding was not considered to be due to GSK2838232 exposure.
- In Part 1A (Cohort 1), Period 3 (Period "3A" for the purpose of differentiating between 100 mg GSK2838232/r vs. 200 mg GSK2838232/r), one subject who had already been dosed on 2 previous occasions (with either GSK2838232 or placebo) was dosed for 2 days with RTV, and then on 05 May 2016 was dosed with either GSK2838232/r or placebo/r as scheduled. On the following day (06 May 2016), the subject experienced an asymptomatic, 6-beat run of NSVT, which was classified at the time as an SAE. Further monitoring, including continuous Holter monitoring revealed no further events. The subject had no troponin elevation throughout the study. After additional investigation it was determined that the NSVT had occurred after the subject had received placebo the previous day. Although the subject had received active on the two prior visits, the protocol allowed for sufficient washout between each dose. Therefore, because the subject had received placebo prior to experiencing the NSVT, the event was not considered to be due to GSK2838232 exposure or a serious and unexpected suspected adverse reaction that would qualify for IND safety reporting.
- In Part 2 (Cohort 6, 200mg/r), a 40 year old male enrolled in the study with no significant medical history experienced an asymptomatic ventricular triplet (NSVT) while asleep at 5:33am on Day 8 (of 11 days worth of dosing) approximately 21 hours after receiving 200 mg GSK2838232/r on the previous day at 8.25am. This event was noted by the site staff and the subject was assessed and found to have no associated clinical symptoms or complaints. The GSK medical monitor was notified. Because the subject was not symptomatic and this did not meet protocol-defined stopping criteria, the study was not unblinded at the time, and the subject was allowed to continue dosing. Dosing in the study is now complete and no further events have been noted. It was the assessment of the site PI and the GSK safety/monitoring team that a ventricular triplet can be seen in healthy volunteers on continuous Holter monitoring. Therefore neither the PI nor GSK considered this event to be a serious and unexpected suspected adverse reaction.

2.2.2.2. Study 204953 (on-going); Pharmacokinetic Data

Study 204953 investigated the safety, tolerability, and PK of escalating doses of GSK2838232 as micronized API, with 100 mg RTV, initially as single doses and then as repeated doses for 11 days.

In addition, it evaluated the relative bioavailability of a single fasted dose of micronized API powder blend in capsules with RTV compared to powder-in-bottle for oral suspension with RTV and the effect of a normal fat meal on the bioavailability of a single dose of GSK2838232 in the capsule formulation with RTV. It will evaluate GSK2838232 exposure after repeated doses of unboosted GSK2838232 in the capsule formulation. Noncompartmental PK analysis was performed using scheduled sample times. This study is ongoing; preliminary results are presented.

Pharmacokinetic analysis was performed on GSK2838232 plasma concentration-time data using nominal time following single doses of 50, 100, and 250 mg in combination with RTV in Part 1A of Study 204953 (Table 3). On average, GSK2838232 Cmax values were reached 4-6 hours after dosing. Terminal half-life values ranged from 15 to 28 hours across the three dose levels. Overall, broad dose proportionality was observed for Cmax and AUC(0-∞) values with ascending single doses of GSK2838232 (50, 100, and 250 mg with 100 mg RTV).

Table 3 Summary of Preliminary Pharmacokinetic Parameter Values after Single Doses of GSK2838232 in Combination with 100 mg Ritonavir (Study 204953, Part 1A)

Dose (mg)	n	t½ (h)	tlag (h)	tmax (h)	Cmax (ng/mL)	AUC(0-∞) (ng.h/mL)
50	8	22.7 (17%) (17.2-28.5)	0.188 (138%) (0-0.5)	3.63 (41%) (2.5-6.0)	17.2 (43%) (8.7-27.9)	458.6 (33%) (210.6-662.0)
100	6	18.0 (14%) (15.8-22.3)	0.167 (155%) (0-0.5)	6.00 (59%) (2.5-12.0)	25.2 (20%) (17.5-31.5)	890.5 (20%) (619.1-1053)
250	5	17.3 (6.4%) (15.5-18.6)	0 (-) (0-0)	5.50 (71%) (2.0-12.0)	60.7 (23%) (40.8-73.1)	1731 (29%) (1222-2505)

Data are presented as mean (CV) (minimum-maximum).

Study 204953 Part 1B was an open label, 2x2+1 three-period, crossover design, evaluating the relative bioavailability of the micronized API GSK2838232 powder blend in capsules compared to the PiB reference formulation for the first two periods, with the assessment of food effect on the capsule formulation in Period 3.

The relative bioavailability of the micronized powder blend in 50 mg hand-filled capsules compared to the micronized API as PiB for oral suspension was assessed as 100 mg GSK2838232 single doses with 100 mg RTV after two pre-doses (48 h) in the fasted state in a randomized crossover design in 12 subjects in the first two periods of Part 1B of Study 204953. Preliminary geometric mean AUC(0-∞) and Cmax values were approximately 45% and 60% higher, respectively, after administration in the capsule formulation compared to oral suspension from PiB (Table 4).

Table 4 Preliminary Assessment of Relative Bioavailability of Capsule Formulation vs. Powder-in-Bottle Formulation of GSK2838232 (Study 204953, Part 1B)

Parameter	Test	Reference	n	Ratio of Geometric Least Square Means	90% CI of Ratio
AUC(0-∞)	Capsule	PiB	12	1.43	(1.194,1.702)
Cmax	Capsule	PiB	12	1.58	(1.312,1.900)

PiB = powder-in-bottle.

The potential food effect with the capsule formulation was assessed as 100 mg GSK2838232 single doses with 100 mg RTV after two pre-doses (48 h) in the fasted state and with a normal fat meal in a non-randomized crossover design (fasted in either Period 1 or 2, fed in Period 3). Eleven subjects provided data for both dietary conditions. Preliminary geometric mean AUC(0-∞) and Cmax values were approximately 60% higher after administration in the capsule formulation with a normal fat meal compared to the fasted state (Table 5).

Table 5 Preliminary Assessment of the Effect of a Normal Fat Meal on GSK2838232 Exposure when Administered as a Capsule Formulation with Ritonavir (Study 204953, Part 1B)

Parameter	n	Capsule – food Geometric mean	Capsule – fasted Geometric mean	Ratio of geometric means (food/fasted)
AUC(0-∞) (ng.h/mL)	11	2414	1539	1.57
Cmax (ng/mL)	11	76.9	47.2	1.63

Repeat dose PK parameter values in Study 204953 Part 2 were determined on Day 1 and Day 11 using nominal time in Part 2 of Study 204953 (Table 6). After the Day 11 dose of GSK2838232 with RTV, exposure (Cmax, AUC[0-τ]) appeared to increase proportionally with the increase in dose level with the PiB and capsule formulations.

Table 6 Summary of Preliminary Pharmacokinetic Parameter Values on Day 1 and Day 11 during Repeated Dosing of GSK2838232 in Combination with 100 mg Ritonavir (Study 204953, Part 2)

Dose (mg)	n	t½ (h)	tlag (h)	tmax (h)	Cmax (ng/mL)	AUC(0-τ) (ng.h/mL)	Cτ (ng/mL)
Study Day 1							
20 (PiB)	6	-	0.417 (49%) (0-0.5)	3.67 (11%) (3.0-4.0)	12.2 (47%) (5.8-20.8)	189.4 (40%) (83.7-284.4)	6.1 (39%) (2.5-8.9)
50 (PiB)	6	-	0.167 (155%) (0-0.5)	3.00 (51%) (2.0-6.0)	18.7 (40%) (9.0-25.9)	288.7 (39%) (138.6-380.2)	9.5 (35%) (5.1-12.6)
100 (capsules)	6	-	0.167 (155%) (0-0.5)	2.25 (23%) (1.5-3.0)	48.4 (32%) (28.1-69.6)	664.1 (31%) (422.5-932.7)	21.6 (33%) (12.8-29.3)
200 (capsules)	6	-	0.083 (245%) (0-0.5)	2.50 (25%) (2.0-3.5)	79.4 (38%) (50.8-125)	1124 (39%) (636.7-1794)	38.9 (36%) (21.7-58.6)
Study Day 11							
20 (PiB)	6	19.2 (16%) (15.1-24.2)	-	5.00 (32%) (2.5-6.0)	27.4 (38%) (11.3-40.4)	474.3 (31%) (214.3-613.2)	15.3 (30%) (7.1-19.2)
50 (PiB)	6	27.3 (52%) (15.2-50.4)	-	3.50 (46%) (1.5-6.0)	58.0 (24%) (40.9-78.0)	1113 (23%) (762.6-1459)	38.8 (29%) (24.5-51.7)
100 (capsules)	6	17.9 (18%) (15.2-23.7)	-	4.00 (40%) (2.5-6.0)	133 (23%) (94.7-164)	2492 (27%) (1624-3301)	81.7 (30%) (45.9-113)
200 (capsules)	6	-[1]	-	3.33 (45%) (1.5-6.0)	240 (38%) (127-368)	4389 (45%) (2095-7161)	151 (46%) (67.8-250)

Data are presented as mean (CV) (minimum-maximum).

1. Concentration data were available up to 24 h after the Day 11 dose, and t½ values were not calculated.

2.2.2.3. Overall Summary/Conclusions of PK data

The original formulation used in the first three studies with GSK2838232 (HMI116787, 200207, and 200912) was SDD. Data from Study 200912 demonstrated that a change to the API formulation of GSK2838232 was feasible for future clinical studies. Study 204953 utilized micronized API powder in a bottle as well as in a capsule. The capsule was shown to be a viable solid dosage form for subsequent studies. A more detailed summary of the data from Study 204953 is in Section 2.2.2.2.

- GSK2838232 SDD did not overall demonstrate significant escalation in exposure from an increase in dose from 100 mg to 200 mg in a cross-study comparison. The API PiB formulation showed a proportional increase in AUC and Cmax for a 2-fold dose escalation from 100 mg to 200 mg.
- The observed tmax of the API form was significantly increased over the SDD formulation (the API formulation also increased tlag relative to SDD).
- The bioavailability of the GSK2838232 API formulation was on average 30-50% of the bioavailability of SDD formulation, but there was a large observed range of relative intra-subject exposures (11-150%).
- Both 10 mg SDD and 20 mg API showed a 10-fold or greater increase in AUC with steady-state RTV (100 mg QD for 10 days) with a smaller (≤4-fold) increase in observed Cmax. The t½ of GSK2838232 increased from 15-18 hours to 34-42 hours in the presence of steady-state RTV, regardless of formulation.
- After single doses of 50 to 250 mg GSK2838232 with RTV, increases in Cmax and AUC(0-∞) values were broadly proportional to the increase in dose. On Day 11 after repeated daily 20 to 200 mg doses of GSK2838232 with RTV, increases in Cmax and AUC(0-τ) values appeared to be proportional to the increase in dose with the PiB and capsule formulations.
- The relative bioavailability of the micronized API powder blend in capsules with RTV was approximately 45%-60% higher than the bioavailability of the micronized API administered as oral suspension from PiB with RTV.
- Co-administration of the micronized API powder blend in capsules with RTV and a normal fat meal resulted in an approximately 60% increase in geometric mean Cmax and AUC(0-∞) values compared to the fasted state with RTV (Study 204953).
- Variability remains fairly constant across formulations and boosted versus unboosted at around 30%-40% (moderate-high).
- Projections of potential future efficacious boosted GSK2838232 API regimens suggest that doses of 20 to 200 mg GSK2838232 API co-administered with RTV will result in mean trough values of at least 3-fold above the derived 90% maximal inhibitory concentration (IC90) target value (5 ng/mL). Even if protein binding has more impact than envisaged and causes a 5-fold increase in IC90 as seen in some preclinical virology studies, the predicted troughs will still be significantly higher than the 5-fold shifted IC90 (25 ng/mL) at doses of 50 mg or higher with RTV.
- The average and maximum AUC/Cmax values observed at the maximum dose studied to date are below NOAEL values in preclinical chronic toxicology studies (6-month rat, 9-month dog).

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To evaluate antiviral activity of GSK2838232/cobi in HIV-1 infected patients during 10-days of monotherapy.	• Maximum decline from baseline (Day 1) in plasma HIV-1 RNA
• To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days.	• Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments.
• To characterize pharmacokinetics (PK) of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days	• GSK2838232 PK parameters following dose administration, as follows: **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Secondary	
• To explore the relationship between GSK2838232 exposure and change in plasma HIV-1 RNA	• GSK2838232 PK parameters Day 10 AUC(0-τ), Cmax, Cτ with Day 11 HIV-1 RNA change from baseline
• To assess the immunologic effect of GSK2838232/cobi when administered over 10 days in HIV-1 infected adults	• Change from baseline in CD4+ cell count to Day 11
• To explore the relationship between GSK2838232 exposure and safety or immunologic parameters, if appropriate.	• GSK2838232 PK parameters on Day 10: AUC(0-τ), Cmax, Cτ with Day 11 change from baseline in CD4+ cell count
• To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if	• Emergence of drug resistance mutations, if appropriate

Objectives	Endpoints
appropriate.	
• To estimate GSK2838232 accumulation and to assess attainment of steady state following administration of GSK2838232/cobi for 10 days in HIV infected subjects.	• **Accumulation:** GSK2838232 PK accumulation ratios (R): Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively • **Steady State:** pre-morning dose concentrations (C0) on Day 2 through 11
• To examine dose proportionality of GSK2838232 PK parameters following GSK2838232/cobi dosing for 10 days in HIV infected subjects.	• Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax and Cτ at different doses levels for the assessment of dose proportionality
Note: Other exploratory objectives and endpoints will be specified in the RAP	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIa, multicenter, open-label, adaptive dose ranging, study to evaluate the antiviral effect, safety, tolerability, and PK of GSK2838232/cobi monotherapy over 10 days in ART-naïve HIV-1 infected adults who are not currently receiving ART therapy. Subjects who have received any ART (including prior MI) therapy will not be eligible for this study. To minimize the number of subjects exposed to suboptimal doses, an adaptive and dose ranging design is applied in this study.

This study consists of a screening visit, a 10-day treatment period, and follow-up evaluations for 2 weeks following last dose.

Screening will be performed as the patients are identified, within 30 days of the first dose of study drug. Eligible HIV-1 infected subjects will receive study treatments for 10 days.

Study Design for 200911

GSK2838232/cobi Once Daily for 10 days[1,2]					
Part A			**Part B**		
Cohort 1	**Dose (mg)**	**Interim Analysis**	**Cohort**	**N**	**(mg)**
N=10	100				
			2	8	200
			3	8	50
			4	8	20

1. Part A Cohort 1 safety/PK/virology data will be evaluated at interim, prior to initiating other cohorts in Part B, which are planned to run in a parallel, randomized fashion. All doses will be given with 150 mg cobicistat.
2. Part B doses are an illustration of the projected doses per cohort. The actual doses for each cohort are subject to modification based upon safety, PK and antiviral activity data from Cohort 1 (Part A). More doses/cohorts (including potential removal of cobicistat co-dosing) may be added. (The maximum dose in Cohort B will not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] is lower in HIV-infected subjects than in healthy subjects at the same dose level).

After successfully completing screening evaluations, the first cohort will enroll 10 subjects to receive the 100 mg GSK2838232/cobi dose. Following interim analysis of Cohort 1, if warranted, Cohorts 2-4 will each enroll 8 subjects to receive a range of GSK2838232/cobi doses.

Day 1 – Day 10: Dosing

Subjects will report to the clinic for outpatient visits in the morning on Days 1 through 10 during the treatment period, except for the weekend (Days 6 and 7). Subjects will arrive each day prior to administration of the morning dose for safety and lab assessments, including HIV-1 RNA blood draws, as described in the Time and Events Table (Section 7.1). Subjects will begin receiving study drug in the morning of Day 1.

Serial, intensive blood PK samples will be collected on Day 1 (up to 24 hours post-morning dose) and Day 10 (up to 96 hours post-morning dose), and limited, single blood PK samples pre-morning doses on Days 3 through 9, except for the weekend. Subjects will be required to fast for 10 hours [overnight] prior to the morning check in on the intensive PK sampling days (Days 1 and 10). All dosing days will require co-administration of treatment with a light snack/meal per cobicistat labeling guidelines. All doses of study medication will be taken with 240 mL of water. Subjects will be required to stay in the clinic on Days 1 and 10 until all specified assessments are completed (12 hours post-dose). Following Day 10, subjects will be required to attend the clinic for follow up assessments including virological and PK blood sampling for up to 3 weeks.

Subjects will be given morning doses on Days 1 through 10 (except for the weekend) in the clinic. Weekend morning doses (Days 6 and 7) will be packaged and sent home for self-administration. After Day 11, the subjects will return frequently for assessments including blood draws for PK and HIV viral load. A diary card will be used to monitor dosing adherence.

Follow-up Visits:

Subjects will return to the clinic on Days 11, 12, 14 (±1 day), and 21 (±1 day) for PK and measurement of HIV-1 RNA levels, viral genotype/phenotype and safety assessments as shown in the Time and Events Table (Section 7.1).

4.2. Type and Number of Subjects

At least 34 subjects will be enrolled such that approximately 6-10 evaluable subjects complete a number of cohorts. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels as appropriate.

If subjects prematurely discontinue the study, additional replacement subjects may be randomised and assigned to the same treatment cohort at the discretion of the Sponsor in consultation with the Investigator.

4.3. Design/Dose Justification

The fastest track to establishing antiviral potential of any novel HIV drug is to study a short course of monotherapy in HIV infected subjects. There is precedent for this across a number of classes of ART drugs.

Uncertainties over the impact of protein binding on the activity of GSK2838232 and the inherent potency of inhibiting the HIV maturation process as a target remain key objectives for the GSK2838232 program. This two-part adaptive design will allow an early understanding of the potential of GSK2838232 in combination with cobicistat (and by implication, RTV), while not exposing HIV-infected subjects to longer courses of what may be suboptimal doses and possible development of resistance.

Early clinical studies have indicated that in order to achieve reasonable IQ values likely to be associated with antiviral efficacy, GSK2838232 will need to be boosted with a pharmacoenhancer, such as RTV or cobicistat (in common with many CYP3A4 substrates).

There is no *a priori* intention to study GSK2838232 unboosted, unless: i) following the preliminary analysis of Part A Cohort 1, there is such pronounced antiviral activity that it would seem the estimates of projected IQ are low, in which case GSK2838232 may be evaluated in a subsequent cohort unboosted, or ii) the data from Cohort 7 in ongoing Study 204953 (planned, GSK2838232 200 mg BID unboosted) support it.

4.3.1. GSK2838232 with Ritonavir

In Study HMI116787, a single dose of 10 mg GSK2838232 (SDD) given after 10 days of RTV 100 mg daily dosing (to steady state) demonstrated an increase in overall exposure (AUC) and Cmax by an average of 10.8- and 2.6-fold, respectively, compared to 10 mg GSK2838232 alone. Terminal phase half-life also increased from approximately 20 hours to 34 hours. This effect was presumably the result of an inhibition of a CYP3A4-mediated pathway. Studies 200912 and 200207 also indicated the utility of RTV in boosting GSK2838232 concentrations.

These data indicate the viability of studying a number of GSK2838232+RTV regimens in this PoC study. Predicted exposures following different GSK2838232 doses with steady-state RTV are presented in Table 7, based on the results of linear regression analyses of the preliminary Day 11 data in Study 204953 (dose levels of 20 to 200 mg) and assuming no significant differences in PK (ADME) between HIV-infected subjects and healthy subjects.

Table 7 Predicted Mean Steady-State GSK2838232 AUC(0-24), Cmax, and IQ, Following Repeated Dose Administration + RTV with Fold Cover to NOAEL

Dose (mg)	Projected AUC24 (ng.h/mL)[1]	Fold cover to NOAEL Dog[2]	Projected Cmax (ng/mL)[1]	Fold cover to NOAEL Dog[2]	IQ[3]
20+RTV	451	36	24	35	3.1
50+ RTV	1127	14	61	14	7.7
100+ RTV	2253	7.2	122	6.9	15
150+RTV	3380	4.8	183	4.6	23
200+RTV	4506	3.6	244	3.5	31

1. Predicted mean values based on linear regression analyses of preliminary Day 11 data in Study 204953.
2. Lowest NOAEL, 20 mg/kg/day obtained from 9-month study in dogs (AUC24 16200 ng.h/mL and Cmax 847 ng/mL)
3. Mean IQs derived from predicted Cτ/IC90 (with target of 5 ng/mL).

Cτ = Pre-dose (trough) concentration at the end of the dosing interval, IQ= inhibitory quotient.

The IQ following 20 mg to 200 mg GSK2838232/r QD is predicted to be >3 to >30-fold above the minimal target value (5 ng/mL) which was derived from preclinical virological assessment as 4 × EC50. No protein binding adjustment has been made because there was a minimal (≤5 fold) shift in assays where the effect of protein was assessed. If protein binding has more impact than anticipated, it is possible that the target Cmin value is approximately 25 ng/mL. In that scenario, projected IQ values at 200 mg/r QD would still be >5.

4.3.2. GSK2838232 with Cobicistat

There have been no preclinical or clinical studies with GSK2838232 and cobicistat to date; however, a review of the literature indicates that pharmacoenhancement of drugs that are known to have dominant CYP3A metabolic pathways is similar with either RTV or cobicistat [Kakuda, 2009; Elion, 2011; Gallant, 2013]. Thus, the use of cobicistat as the CYP3A4 inhibitor pharmacoenhancer in this Phase IIa study in place of ritonavir is expected to produce a similar profile of GSK2838232 ADME (and therefore systemic exposure). The pharmacokinetic data available after Part A Cohort 1 will confirm this assumption.

4.3.3. Interim Analysis

An evaluation of GSK2838232 safety, efficacy and PK data will be done after Part A Cohort 1, if the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects and the Bayesian probability

from Cohort 1 is less than 70%, the study will not move forward into Part B, otherwise doses will be selected for evaluation in Part B. If pharmacokinetic exposure after the 100 mg GSK2838232/cobi dose is in the range of values observed after 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) doses. The highest dose tested in Part B will be selected to result in exposures similar to those seen with 200 mg/r in Study 204953.

4.4. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2838232 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.4.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2838232		
Cardiovascular	Pre-clinical studies have shown the following findings: elevated heart rates, an isolated episode of non-sustained ventricular tachycardia and minimal to mild, sporadic troponin I elevations in dogs. A subsequent investigative cardiovascular study in telemetered dogs treated for 4 weeks did not replicate these effects. Isolated microscopic cardiovascular changes were noted (focal extramural arteritis and localized epicardial inflammation), however these changes were considered of uncertain relationship to GSK2838232 because similar findings occur at low incidence in normal beagles and there were no GSK2838232-related functional changes by telemetry and echocardiography, or changes in cTpnI and NTproBNP. In addition there was no correlation between histologic changes and plasma exposure or heart tissue concentrations of GSK2838232. 3, 6 and 9 month toxicology studies in rat and dog did not demonstrate any evidence of cardiovascular injury or impact on cardiovascular function. In the four GSK2838232 studies conducted so far there was no pattern of cardiovascular changes of clinical significance related to GSK2838232 and no clinically significant abnormality in electrocardiogram values other than the two SAEs documented and discussed. Review of published bevirimat preclinical and clinical safety data indicates no significant toxicities or AEs of interest, other than a 30% incidence of gastrointestinal symptoms (including diarrhea). There were no significant cardiovascular AEs reported in published clinical studies.	Subjects will be clinically monitored for any signs of myocardial injury (chest pain, shortness of breath, pain with inspiration), elevated heart rate or arrhythmias. Samples for the assessment of troponin will be taken. Baseline EKG and Holter (to use for screening and for later comparisons if needed) Exposures of GSK2838232 will be closely monitored in the clinical study so as to not exceed pharmacokinetic stopping criteria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Cobicistat (Tybost)		
General	The cobicistat label includes the following information: TYBOST decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect should be considered when interpreting changes in estimated creatinine clearance in patients initiating TYBOST In one study investigating cobi+(atazanavir and tenofovir DF/emtricitabine) vs RTV+(atazanavir and tenofovir DF/emtricitabine), a higher frequency of reports of jaundice (6% and 3%) and ocular icterus (4% and 2%) were reported in the cobi group compared to the RTV group. Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides have been observed. The implications of these findings are unknown. The vast majority of available safety data has been obtained in combination studies with other ART. There are no warnings of obvious cobicistat-related adverse events or safety concerns.	Subjects will be closely monitored for any signs or symptoms potentially associated with cobicistat administration, in particularchanges in serum creatinine and liver chemistry.
HIV-1 Infection/Patient population		
HIV Resistance Propensity for co-meds and possible DDIs	HIV Drug Resistance to unique mechanism Recognize HIV patients have a higher chance of comorbidities/diseases and a risk of taking a medicine or product contraindicated in the study	Closely monitor HIV viral load and genotypic resistance Strict adherence to protocol criteria around concurrent meds

4.4.2. Benefit Assessment

This study in HIV-1 infected but otherwise healthy subjects is a 10-day monotherapy design. It is anticipated that all subjects receiving GSK2838232 will experience anti-HIV effects whereby their (blood) HIV viral titres are reduced, until administration stops and the viral load returns to baseline levels. There is no expected longer term anti-HIV benefit to administration of GSK2838232. Participation in this study contributes to the process of developing GSK2838232 and other new therapies for the treatment of HIV infection.

4.4.3. Overall Benefit:Risk Conclusion

To date, 53 healthy subjects have received GSK2838232 in three completed studies. One study (204953) is ongoing (52 healthy subjects have completed this study so far).

Subjects have received single doses up to 200 mg SDD alone (studies HMI116787 and 200912), 250 mg API in combination with RTV (204953), and then in repeated daily doses of up to 50 mg SDD alone (200207) for 5 days or 200 mg in combination with RTV (204953) for 11 days.

There have been two cardiovascular SAEs reported from clinical studies where the subject was receiving GSK2838232 to date (one in 200207, one in 204953). Neither is thought likely to be due to GSK2838232.

There have been no other withdrawals due to drug-related AEs and no trends relative to laboratory toxicity. One subject was withdrawn in Part 1A of 204953 because of low haemoglobin lab values, thought unrelated to study drug or study procedures.

With respect to CV effects, with the exceptions noted, there have been no clinically significant changes in troponin, heart rate, blood pressure, ECG, or telemetry monitoring.

Subjects will also be at risk for AEs from cobicistat use and will be monitored closely for such events.

Given the preclinical profile and the clinical profile to date, the overall risk to HIV-1 infected but otherwise healthy subjects at the proposed GSK2838232 doses (with or without cobicistat) for 10 days is predicted to be low. Mean exposures at the highest dose studied are not projected to exceed NOAEL values obtained in chronic toxicology studies, further reducing potential risk.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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.

Approximately 10-12 HIV-1 infected subjects will be enrolled into Part A. If warranted by an interim safety, virology and PK data analysis, approximately 8 subjects will be enrolled in each of Cohorts 2-4 in Part B, which will be a parallel group design. Eligible patients are those who are ART-naïve and who are not currently receiving ART therapy.

Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels or configurations (e.g., GSK2838232 alone).

If subjects prematurely discontinue the study, additional subjects may be enrolled as replacement subjects and assigned to the same treatment at the discretion of the Sponsor.

5.1. Inclusion Criteria

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

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy (other than HIV infection) male or female as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. Defined as no other chronic medical conditions and taking no chronic medications.
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.
4. A creatinine clearance >80 mL/min as determined by Cockcroft-Gault equation [Cockcroft, 1976] CLcr (mL/min) = (140 – age) * Wt / (72 * Scr) (times 0.85 if female) where age is in years, weight (Wt) is in kg, and serum creatinine (Scr) is in units of mg/dL.
5. Confirmed HIV positive; CD4+ cell count ≥350 cells/mm3 and plasma HIV-1 RNA ≥5000 copies/mL at Screening.
6. No current and no prior ART.

WEIGHT
7. Body weight ≥ 50 kg (110 lbs.) for men and ≥45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive)

SEX

8. Male or Female
 	
A female subject of reproductive or non-reproductive potential is eligible to participate if she is not pregnant (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test at screening and prior to first dose), not lactating, and at least one of the following conditions applies:
 	
Reproductive potential:
 	
Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. They will be counselled on safer sex practices
 	
There is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.
 	
Fertile females, who have an established, long-term lifestyle of sexual abstinence, or only same sex partners, require no other means of birth control.
 	
Non-reproductive potential:
 	
• Pre-menopausal females with one of the following:
  • Documented tubal ligation
  • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  • Hysterectomy
  • Documented Bilateral Oophorectomy
• Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
 	
Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until one week after the last dose of study medication.
 	
a. Vasectomy with documentation of azoospermia.
 	
b. Male condom plus partner use of one of the contraceptive options below:
  • Contraceptive subdermal implant that meets the SOP effectiveness criteria

including a <1% rate of failure per year, as stated in the product label

- Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
- Oral contraceptive, either combined or progestogen alone or Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

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.

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

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Alanine aminotransferase (ALT) and BIL >1.5xupper limit of normal (ULN; isolated BIL >1.5xULN is acceptable if BIL is fractionated and direct BIL <35%).
2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); HBV and/or HCV positive.
3. Subjects who have any other chronic medical condition, including CV, respiratory, neurologic, psychiatric, renal, gastrointestinal (GI), oncologic, rheumatologic, or dermatologic
4. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.

CONCOMITANT MEDICATIONS
5. 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 GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

RELEVANT HABITS
6. History of regular alcohol consumption within 6 months of the study defined as: • An average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of 80 proof distilled spirits. 7. Smoking is an exclusion criteria for this study. Urinary cotinine levels indicative of smoking at screening. 8. Chronic marijuana or use of other elicit medications (cocaine, heroin) is an exclusion criteria.

CONTRAINDICATIONS
9. 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
10. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. 11. Screening or baseline cardiac troponin I greater than the 99% cutoff (>0.045 ng/mL by the Dimension Vista CTNI assay). 12. A positive pre-study drug/alcohol screen. 13. Prior history of receiving an HIV maturation inhibitor 14. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. 15. 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). 16. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

17. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 30 days of study drug administration or anticipated need for such treatment within the study.
18. Treatment with immunomodulating agents (such as systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (such as hydroxyurea or foscarnet) within 30 days of study drug administration.
19. An active Center for Disease Control and Prevention (CDC) Category C disease except cutaneous Kaposi's sarcoma not requiring systemic therapy during the trial.
20. Treatment with any vaccine within 30 days prior to receiving study medication.
21. Exclusion Criteria for 24-Hour Screening Holter:
    - Any symptomatic arrhythmia (except isolated extra systoles).
    - Sustained cardiac arrhythmias (such as atrial fibrillation,flutter or supraventricular tachycardia (≥10 seconds)
    - Non-sustained or sustained ventricular tachycardia (defined as ≥3 consecutive ventricular ectopic beats).
    - Any conduction abnormality including but not specific to left or complete bundle branch block, atrioventricular [AV] block, high grade or complete heart block Wolff-Parkinson-White [WPW] syndrome etc.).
    - Sinus Pauses >3 seconds.

22. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<45 and >100 bpm	<50 and >100 bpm
PR Interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
*QTc interval	>450 msec	

*The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read. The specific formula used to determine eligibility and discontinuation for an individual participant in 204953 will be Fridericia's formula.

- *Note: A heart rate from 100 to 110 beats per minute (bpm) can be rechecked by ECG or vitals within 30 minutes to verify eligibility.*
- Evidence of previous myocardial infarction (Does not include ST segment changes associated with repolarization).
- Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], WPW syndrome).
- Sinus Pauses >3 seconds.

- Any significant arrhythmia which, in the opinion of the principal investigator OR GSK medical monitor, will interfere with the safety for the individual subject.
- Non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats).

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 any SAEs.

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".

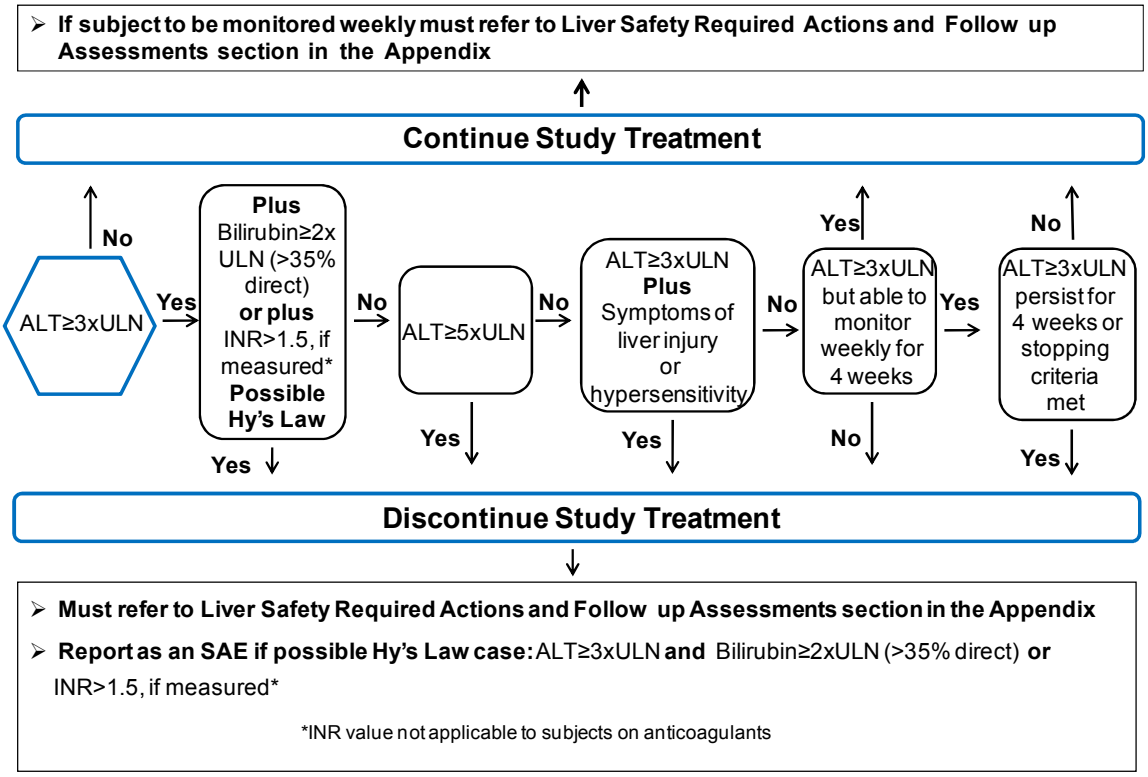
A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the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

5.4.1. 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).

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

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2, Section 12.2 and Section 12.3.

5.4.1.1. 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.

5.4.2. QTc Stopping Criteria

- The *same* 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.
  - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
  - Once the QT correction formula has been chosen for a subject's eligibility, the *same 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 ECGs obtained over a brief (e.g., 5-10 minutes) recording period.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

5.5. Stopping criteria based on Adverse Events

Any grade 3 or higher treatment-related adverse events that occur in ≥2 subjects will be carefully reviewed and if considered clinically significant, dosing will be halted pending further discussion with the FDA. Any single treatment-related SAE will also trigger immediate evaluation and reporting processes in accordance with applicable regulations.

5.6. 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.

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Formulation description:	GSK2838232 powder blend in a capsule	Tablet
Dosage form:	Swedish orange, unmarked capsules (50 mg), and white, unmarked capsules (10 mg)	Orange, round, biconvex, film-coated tablets debossed with "GSI" on one side and plain faced on the other side providing 150 mg of cobicistat.
Unit dose strength(s)/ Dosage level(s):	50 mg capsule for 200 mg, 100 mg, 50 mg doses and 10 mg capsule for 20 mg doses	150 mg for 150 mg doses

	Treatment	
Product name:	**GSK2838232 Capsule (API)**	**Tybost (cobicistat, cobi) tablet**
Route/ Administration/ Duration:	Administered orally QD for 10 days	Administer orally, QD for 10 days
Dosing instructions:	Administer with light meal and 240 mL of water.	Administer with light meal and 240 mL water.
Manufacturer/ source of procurement:	GSK	Gilead
Method for individualizing dosage:	Capsules supplied in high-density polyethylene bottles for individualized dosing by the clinic	Capsules supplied in bulk containers for individualized dosing by the clinic

6.2. Treatment Assignment

Subjects will be assigned to treatment (active) in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

6.3. Planned Dose Adjustments

Following the interim analysis of safety, virology and PK data from the first cohort of subjects in Part A, the option to adjust dose levels from those described exists. No dose will be administered that has an associated projected mean AUC or Cmax value higher than the most conservative NOAEL obtained from the chronic toxicity studies (i.e., from the 9-month dog toxicity study described in Section 2.2.1).

6.4. Blinding

This will be an open-label study. Treatment allocation in Part B will be randomised (to GSK2838232 dose level).

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for capsule/tablet storage and dispensing will be detailed in a Study Specific Technical Agreement/Memo or Pharmacy Manual, which will be accompanied by a Quality Agreement.

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.
- A Material Safety Data Sheet/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.

6.7. Compliance with Study Treatment Administration

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.

When subjects self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed through querying the subject during the site visits and documented in the source documents and case report form (CRF). A record of the number of study treatment(s) dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK2838232 >200 mg+cobicistat within a 28-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose; however, in the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities until GSK2838232 can no longer be detected systemically (at least 10 days for GSK2838232)

- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)
- 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.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.10. Lifestyle and/or Dietary Restrictions

6.11. Contraception

Female subjects can be of childbearing or non-child bearing potential.

Females of reproductive potential may only be enrolled if they are using two forms of complementary contraception, which must include one barrier method. There is no definitive DDI information with GSK2838232 and an interaction with oral contraceptives is possible, so other (barrier, inter-uterine device etc.) methods of contraception will be required.

Females of reproductive potential, who have an established, long-term lifestyle of sexual abstinence, or only same sex partners, require no other means of birth control.

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until one week after the last dose of study medication:

1. Vasectomy with documentation of azoospermia. 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.

OR

2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring

- Percutaneous contraceptive patches

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.

6.12. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice from 7 days prior to the first dose of study medication until after the final dose.
- Doses will be given in the fed state (light breakfast), following overnight fasting (>10 hours). Lunch will provided ≥4 hours after the dose; water will be allowed ad libitum throughout.

6.13. Caffeine, Tobacco and Exercise

- Subjects should refrain from alcohol for 48 hours before screening and then for 48 hours prior to admission and baseline assessments (on Day 1). Alcohol is then not permitted for the duration of the treatment period (through Day 10) and until the final follow-up visit.
- Use of tobacco products is not allowed from screening until after the final follow-up visit
- Subjects will abstain from strenuous exercise for 72 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.14. Concomitant Medications and Non-Drug Therapies

- Subjects must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur at Screening and Day -1 for each treatment period. A positive result will lead to exclusion from the remainder of the study.
- The Principal Investigator must be informed as soon as possible about any medications taken from the time of screening until the subject is discharged from the study. Over-the-counter medications will not be permitted during the treatment period except as needed to treat an AE. If medication is needed, use should be restricted to 4 hours after dosing if possible.

6.14.1. Permitted Medications and Non-Drug Therapies

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

6.14.2. 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.

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 (Section 7.1), 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. In overview, subjects will be screened, begin dosing and then continue assessments through and for up to 2 weeks after the completion of dosing.

The following points must be noted:

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

    1. 12-lead ECG
    2. vital signs
    3. blood draws.

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

7.1. Time and Events Table

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
Informed Consent	X																
Review inclusion/exclusion	X		X														
Demography including height, weight and BMI	X																
Brief physical			X														
Medical/medication/ drug/alcohol history	X		X														
CDC Classification	X		X													X	X
Prior antiretroviral therapy	X																
12-lead ECG[3]	X		X			X	X			X		X		X		X	X
Holter (24 hr)	X																
Vital signs[4]	X		X			X	X			X		X		X		X	X
Drug screen	X		X			X						X				X	
Hepatitis B Surface antigen and hepatitis C antibody testing	X																
Serum or urine β-hCG (WoCBP only)	X		X														X
Clinical lab tests (inc troponin)	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Fasting lipid panel	X																X
AE assessment[5]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Con Medication Review	X		X	X	X	X	X			X	X	X	X	X	X	X	X
HIV-1 RNA PCR[6]	X		X	X	X	X	X			X	X	X	X	X	X	X	X
Lymphocyte subsets[7]	X		X										X				
Plasma for genotype/phenotype[8]			X			X	X			X			X			X	X
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		X
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
AE enquiry[13]			X	X	X	X	X			X	X	X	X	X	X	X	X
Telephone call to IVRS[14]	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

1. Screening will occur within 30 days prior to the first dose of study drug.
2. Table is set up for the weekend during dosing to occur on Days 6 and 7. If the weekend occurs on Days 5 and 6, perform all "Day 5" assessments on Day 7.
3. On Day 1, ECGs (x2) will be performed pre-dose , and then 1, 1.5, 2, 3, 4 and 6 hours post dose. The pre-dose ECGs should be performed at least 5 minutes apart and preferably within 1 hour prior to dose. On Days 4, 5 and 8, ECGs will be obtained prior to morning dosing and at 2, 4 and 6 hours post-dose. On Day 10, ECGs (x2) will be performed pre-dose, and then 1, 1.5, 2, 3, 4 and 6 hours post dose. On Day 11, an ECG will be obtained prior to the 24-hour PK sample.
4. BP, RR, HR and temperature will be obtained at Screening (x1) and Day 1 pre-dose (x2). BP and HR will be obtained on Day 1 at 2 hours post-morning dose and on Days 4, 5 and 8 pre-dose. BP and HR will be obtained on Day 10 at pre-dose and 2 hours post-morning dose, and at Follow-up.
5. Only SAEs related to study participation will be collected between screening and Day 1.
6. On Days 1-5 and 8-10 samples for HIV-1 RNA PCR collected before morning dose. On Days 1, 10 and 11 two samples for HIV-1 RNA PCR will be collected 5-30 minutes apart.
7. Lymphocyte subsets by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+and CD8+counts).
8. Blood samples for phenotype and genotype will be collected at pre-dose on Days 1, 4, 5 and 8 in the morning on Day 11 and at follow-up.
9. Serial plasma samples (2 mL) for determination of GSK2838232 will be collected on Day 1 and Day 10 at pre dose (within 15 minutes prior to dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-am dose. Pre-dose PK samples (within 15 minutes prior to dose) will be taken on the mornings of Days 3, 4, 5, 8 and 9 and a single sample will be taken on Days 12 and 14.
10. Samples (2 x 0.5mL) of plasma for assessment of immunological markers at screen, baseline (pre-dose) and day 11
11. Subjects will receive a single dose of GSK2838232 and cobicistat each morning with a light breakfast meal and 240 mL of water from Day 1 to Day 10. Doses taken in the clinic will be administered after an overnight fast of at least 10 hours .On Days 6 and 7, doses will be self administered but confirmed by phone
12. PGx sample should be collected on Day 1.
13. An AE enquiry will be made at each visit, subjects will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status
14. A screening/registration call should be made to the IVRS to register the subject at screening. An additional call will be made to document a screen failure. A randomization call should be made to the IVRS system approximately one week prior to scheduled Day 1. Note: The randomization call must be made in order to have study drug on site for Day 1. Additional calls will be made every day that the subject has a scheduled study visit to the clinic. If a subject terminates the study prematurely a call should be made to the IVRS
15. Only if early termination visits occur during the treatment period.

AE = Adverse event; CDC= Center for Disease Control and Prevention; ECG = Electrocardiogram; ET = Early termination; hCG = Human chorionic gonadotrophin; HIV = Human immunodeficiency virus; IVRS= Interactive Voice Response System; PCR = Polymerase chain reaction; PK=Pharmacokinetic.

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.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.2.1. Holter Monitoring (Screening criteria)

The 24-hour Holter monitoring should only be performed at Screening after the subject has met all other inclusion criteria.

Analysis of the Holter tapes will consider the following:

- Heart rate (brady and tachycardia)
- Normal and aberrant beats
- Number of supraventricular contractions, premature atrial contractions, premature ventricular contractions, couplets, triplets, and ventricular tachycardias
- Atrio-ventricular conduction defects
- Atrial fibrillation and flutter.

7.3. Efficacy

7.3.1. HIV-1 RNA Sampling

Plasma for quantitative HIV-1 RNA will be collected at timepoints listed in the Time and Events Table in Section 7.1. To reduce sample variability, two plasma HIV-1 RNA samples will be collected on Days 1, 10, and 11.

An HIV-1 RNA PCR assay with a lower limit of detection (LLOD) of 50 copies/mL (ultrasensitive assay) will be used for post-baseline assessments. An HIV-1 RNA PCR assay with a LLOD of 400 copies/mL (standard assay) will be used for screening and baseline assessments and will include a re-test with and ultrasensitive assay for all baseline values below the LLOD. An HIV-1 RNA PCR assay with a LLOD of 2 copies/mL (supersensitive assay) may be used for exploratory analysis.

7.3.2. Lymphocyte Subsets by Flow Cytometry

Whole venous blood samples will be obtained from each subject for the analysis of lymphocyte subsets by flow cytometry at the timepoints listed in the Time and Events Table in Section 7.1.

Details concerning the handling, labeling and shipping of these samples will be supplied separately.

7.4. Safety

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

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

The definitions of an AE or SAE can be found in Appendix 5, Section 12.5.

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

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

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1). An AE enquiry will be made at each visit, where subjects will be specifically asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5, Section 12.5.
- 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 5

7.4.1.2. 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?"
- "Have you experienced any alteration in personality, behaviour, mood or any altered mental status?"

7.4.1.3. 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, and non-serious AEs of special interest (as defined in Section 12.5) 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 5.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 5 (Section 12.5.3) and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

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

The following disease-related events (DREs) are common in subjects with HIV-1 infection and can be serious/life threatening:

- events or outcomes listed in the CDC Classification System for HIV-1 Infections (see Appendix 9; Section 12.8)
- sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a serious adverse event).

These events will be recorded on the DRE page in the subject's CRF using the HIV Associated Conditions eCRF. These DREs will be monitored by the medical monitor and study team on routine basis.

However, if any of the following conditions apply, then the event should be reported as an SAE using the standard process:

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject,
  or
- The Investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.
  or
- Death occurring for any reason during a study, including death due to a disease related event, will always be reported promptly.

If either of the above conditions is met then record the DRE on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly to GSK.

7.4.1.6. Regulatory Reporting Requirements for SAE

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs 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.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until one week post study
- If a pregnancy is reported then the investigator should inform GSK within 24hrs of learning of the pregnancy and should follow the procedures outlined in Appendix 7, Section 12.6.

7.4.3. Physical Exams

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

7.4.4. Vital Signs

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

7.4.5. Electrocardiogram (EGC)

- Triplicate 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.4.6. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments as defined in the Tables below must be conducted in accordance with the SRM and Protocol Time and Events Schedule (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled 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 SRM. 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 SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory:

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered in the CRF.

Haematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed below.

Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential</u>:</td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes with T-cell subsets</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Bicarbonates</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
<tr><td>Troponin I</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravity
• pH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td>• HIV
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)
• FSH and estradiol (as needed in women of non-child bearing potential only)
• Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
• Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]</td></tr>
</table>

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 12.2 and Section 12.3
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 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.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for analysis of GSK2838232 concentrations will be collected at the time points indicated in Time and Events Tables (Section 7.1).

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.5.2. Sample Analysis

Plasma analysis will be performed by Covance, Madison under the control of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS, GlaxoSmithKline. Concentrations of GSK2838232 will be determined in plasma using the currently approved bioanalytical methodology.

Once the plasma has been analyzed for GSK2838232 any remaining plasma may be analyzed qualitatively for other circulating metabolites and these results would be reported under a separate PTS protocol.

Raw data will be archived at the Covance, Madison facility.

7.6. Biomarker(s)/Pharmacodynamic Markers

7.6.1. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide plasma for viral genotype and phenotype analysis, at the times listed in the Time and Events Table in

Section 7.1. Details concerning the handling, labeling and shipping of these samples will be supplied separately.

Genotypic and phenotypic analyses will be carried out by Monogram Biosciences using their GAG/PR and PR/RT formats, in which PCR amplification is used to generate HIV cDNA products including the Gag and the PR and RT coding regions, respectively. Phenotypic analyses of the GAG/PR region will include susceptibility to GSK2838232 . Analysis will be done on Day 1 and Day 11 samples. In the case of rebound HIV-1 viral load, analysis will be completed on samples corresponding to time point of rebound occurrence.

7.7. Genetics

Information regarding genetic research is included in Appendix 4, Section 12.4.

7.8. Value Evidence and Outcomes

Not required.

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 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

The primary objectives of this study are to investigate the safety, tolerability, and antiviral activity of GSK2838232 administered as monotherapy in combination with cobicistat in HIV-1 infected subjects, over a 10 day treatment period. The antiviral activity will be assessed by estimating plasma HIV-1 RNA max change from baseline during the study.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size for this study is based primarily on feasibility to provide adequate precision for the estimations.

Based on data from the short term monotherapy study of BMS-955176 PoC (AI468002) study and assuming viral load values for individual subjects follow a log-normal distribution, 1000 trial simulations in Fixed and Adaptive Clinical Trial Simulation (*FACTS*) software were conducted from the distribution with mean of change from baseline viral load drop on log scale at 1.0 to 1.5 copies and SD=0.4 and sample sizes=10 for Part A. Using Bayesian calculation with non-informative priors for the mean and weakly informative priors for the error parameters, Normal (0, 100) for mean and Inverse Gamma (0.35, 0.0875) for error parameters, the posterior probability to achieve a cutpoint 1.2 log was calculated for each simulated trial, and percentage of the trials with posterior probability of viral load<-1.2log drop given true mean) ≥70% were calculated and are shown below in Table 8.

Table 8 Percentage of the trials with posterior probability>=70% for Part A

True Mean	Cutpoint	Posterior Prob>=70%
1.0	1.2	1.4%
1.1	1.2	9%
1.2	1.2	29%
1.3	1.2	59%
1.4	1.2	83%
1.5	1.2	96%

An Emax model with functional uniform priors [Bornkamp, 2014] was conducted using simulated data combining Part A and Part B with all doses. Success is defined as a posterior probability of the highest dose to achieve a cutpoint 1.2 log reduction in viral load. This was calculated for each simulated trial and the percentage of the trials with posterior probability greater or equal to 70% were also calculated and are shown below (Table 9). The table lists different viral load drop scenarios. The last scenario assumes the flat drop for all doses are 0.5. This scenario reflects the null hypothesis of no treatment effect. In this scenario 0% of the trials achieve the pre-specified decision rule for success.

Table 9 Percentage of the trials with posterior probability ≥70%

Cutpoint	Posterior Prob≥	Part A+ Part B mean VL drop for doses 200, 100, 50, 20	Part A+ Part B
1.2	70%	1.5, 1.4, 1.2, 0	99%
		1.5, 1.4, 1.2, 0.5	96%
		1.5, 1.4, 1.0, 0.5	93%
		1.5, 1.3, 1.2, 0.5	86%
		0.5, 0.5, 0.5, 0.5	0%

9.2.2. Sample Size Sensitivity

Similar simulations in FACTS were conducted from the distribution with mean of change from baseline viral load drop on log scale at 1.5 copies and SD=0.4 or 0.6 and sample sizes of 6-8 or 10 for Part A. Using Bayesian calculation, the posterior probability to achieve a cutpoint 1.2 log (in Table 10) was calculated for each simulated trial, and percentage of the trials with posterior probability greater than or equal to 70% was calculated and are shown below.

Table 10 Percentage of the trials with posterior probability ≥70% for Part A

True Mean	Cutpoint	Posterior Prob≥	Std for log10 VL	N=6	N=8	N=10
1.5	1.2	70%	0.4	90%	94%	96%
			0.6	75%	81%	84%

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Intent to Treat Exposed Population (ITT)
The ITT-Exposed Population is defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received at least 1 dose of treatment and at least one post-baseline HIV-1 RNA measurement. This will be the primary population for the final efficacy analysis for all active treatment groups.

Per Protocol Population (PP)
The Per Protocol Population is defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received all doses and all post-baseline HIV-1 RNA measurement, with exceptions of major protocol deviation.

Safety Population

The Safety Population is defined as all subjects who are enrolled into the study with documented evidence of having received at least 1 dose of randomized treatment.

Pharmacokinetic Population

The PK Population will include all subjects who receive GSK2838232 and undergo plasma PK sampling during the study. Subjects for whom a plasma PK sample is obtained and assayed will be included in the listing of plasma GSK2838232 concentration-time data. Results from samples collected from a subject with emesis occurring within 4 hours of the dose will not be considered as evaluable.

9.3.2. Interim Analysis

An interim analysis of preliminary safety, tolerability, PK and antiviral activity will occur after subjects of Part A Cohort 1 complete their Day 13 visit. If based on this review the Cohort 1 dose is determined to be the highest dose (e.g. the exposure level of GSK2838232 is in the range of the maximum GSK2838232 exposure seen previously in healthy subjects), the Bayesian posterior probability that the log10 viral load decline from baseline is greater than a cut-point will be calculated. If the Bayesian probability from Cohort 1 is less than 70% this will provide evidenceto not move forward into Part B. Otherwise, the study team will review the data in order to make a dose selection decision for the subsequent Part B Cohorts. If the pharmacokinetic exposures after the 100 mg GSK2838232/cobi dose look similar to those obtained with 100 mg GSK2838232/r in prior studies, the doses for Part B will be extended to both lower (20 mg, 50 mg) and higher (200 mg) doses.

Maximum change and change from baseline in plasma HIV-1 RNA will be summarized by treatment or by assessment day. The proportion of subjects with plasma HIV-1 RNA < 400 and < 50 copies/mL will be summarized by treatment and assessment day. The analyses will be done for both PP and ITT exposed population if two populations are not the same.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The 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 will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and %CVb for continuous variables, 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 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures,

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

9.4.1.1. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library standards and data will be in CDISC format. No formal statistical analysis of the safety data will be conducted.

9.4.1.2. Efficacy Analyses

Both the PP and ITT Populations will be used for all efficacy analyses if there are dropouts. Plasma HIV-1 RNA max change and change from baseline during the study will be calculated for each subject on each assessment day.

Plasma HIV-1 RNA will be listed by treatment, subject, and assessment day and summarized by treatment and assessment day along with change from baseline.

Plots of mean and median plasma HIV-1 RNA actual and change from baseline data will be generated by treatment and assessment day.

- Plasma HIV-1 RNA change from baseline to the on-treatment nadir (maximum change) will be calculated for each subject and summarized by treatment.

Together, the data from Parts A and B will investigate the complete dose-response curve and the impact of lower doses on potential development of resistance. A dose-response curve will be fit to the data from Parts A & B using functional uniform priors.

9.4.1.3. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling and Simulation Department, GlaxoSmithKline. Plasma GSK2838232 concentration-time data will be analyzed by non-compartmental methods with WinNonlin Version 6.1 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:

Plasma GSK2838232 Pharmacokinetic Parameters to be Estimated:

Study Day	Parameters
1	AUC(0-24), Cmax, tmax, tlag, C24
10	AUC(0-τ), Cmax, tmax, t½, C0, Cτ, CL/F, R_AUC, R_Cmax, R_Cτ

Results based on samples collected from a subject with emesis within 4 hours of the dose will not be considered as evaluable.

All PK data will be stored in the R&D archives, GlaxoSmithKline.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline. Details of the statistical analyses will be provided in the RAP. An outline is provided below:

Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. Plasma GSK2838232 PK parameters, with the exception of tmax and tlag, will be log-transformed prior to analysis.

Dose proportionality of plasma GSK2838232 PK parameters from Day 1 [AUC(0-24) and Cmax] and Day 10 [AUC(0-τ) and Cmax] will be assessed using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI. The accumulation ratio (R) and steady-state assessments will be performed, if quality of the data permits. Comparisons of Day 10 with Day 1 PK for each dose will be used for the accumulation ratio (R) evaluation. Pre-dose concentrations between Days 7-10 will be used for steady-state assessment.

9.4.2. Secondary Analyses

9.4.2.1. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between various PK parameters (e.g., AUC, Cmax, Cτ, etc.) and PD measures (e.g., log10 reduction from baseline in plasma HIV-1 RNA on Day 11 or safety parameters) will be explored using various models including Emax. The relationship between dose and PD measures will also be explored. Details of the PK/PD exploratory analyses will be provided in the RAP.

9.4.2.2. Viral Genotyping and Phenotyping Analyses

Viral genotypic/phenotypic data will be listed and descriptive summaries will be provided. Details of the analyses will be provided in the clinical virology report.

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 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.

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.

10.8. Review Committees

The Safety Review Team (SRT) is a GSK cross-functional team reviewing all available safety data related to the project, including in-stream data from this study, in an ongoing manner. The SRT is an internal GSK requirement put in place to ensure holistic evaluation of the safety profile of an investigational product with systematic, periodic and documented reviews of available safety data, with the appropriate communication and escalation of new findings that have the potential to impact patient safety

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

µg/mL	Microgram per millilitre
ABC	Abacavir
AE	Adverse Event
AIDS	Auto immunodeficiency syndrome
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredient
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUC(0-24)	Area under the concentration-time curve from zero (pre-dose) to 24 h
AUC(0-48)	Area under the concentration-time curve from zero (pre-dose) to 48 h
AUC(0-t)	Area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration
BCRP	Breast cancer resistance protein
Bpm	beats per minute
BVM	Bevirimat
BIL	Bilirubin
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
C24	24 hour trough concentration
CDC	Center for Disease Control and Prevention
CI	Confidence interval
CL/F	Oral Clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CPK	Creatine Phosphokinase
CRF	Case report form
cTnI	Cardiac troponin I
CV	Coefficient of variation
CVb	Between-subject variability
CYP	Cytochrome P450
DDI	
DNA	Deoxyribonucleic acid
EC50	50% protection against resistant mutant HIV infection
ECG	Electrocardiogram

FC	Fold Changes
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FTIH	First time in Human Study
g	Gram
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour(s)
HBsAg	Hepatitis B surface antigen
hcG	Human chorionic gonadotrophin
HDPE	High density polyethylene
hERG	Human Ether-a-gogo Related Gene
HIV	Human Immunodeficiency Virus
IC50/90	50% or 90% maximal inhibitory concentration
IEC	International Ethics Committee
IQ	Inhibitory quotient
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous
IVRS	Interactive voice response system
kg	Kilogram
L	Litre
LLOD	Lower limit of detection
MC	Melanocortin
MedDRA	Medical Dictionary for Regulatory Activities
mg/mL	Milligram per millilitre
MI	Maturation inhibitor
mL	Milliliter
mRNA	messenger Ribonucleic Acid
ND	Not done
ng/mL	Nanogram per millilitre
nm	Nanometer
NO	Not observed
NOAEL	No Observed Adverse Effect Level
NTproBNP	N-terminal prohormone of brain natriuretic peptide
NSVT	Non-sustained ventricular tachycardia
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBL	Peripheral Blood Lymphocytes
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamics
P-gp	P-glycoprotein
PHIV	Pseudo- HIV
PiB	Powder-in-bottle
PK	Pharmacokinetic

PoC	Proof of Concept
PI	Protease Inhibitor
RAP	Reporting and analysis plan
RT	Reverse Transcriptase
SAE	Serious adverse event
SDD	Spray Dried Dispersion
SRM	Study reference manual
t1/2	Terminal elimination half-life
TEM	Transmission Electron Microscopy
tlag	Time of first quantifiable concentration
tmax	Time of occurrence of Cmax
U	Units
UGT	Uridine 5'-diphospho-glucuronosyltransferase
Vz/F	Mean apparent oral volume of distribution
WPW	Wolff-Parkinson-White

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Abbot, Roche HIV kit
Chiron RIBA
Inform
Monogram
Phoenix WinNonlin
SAS
Tybost (cobicistat)

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

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

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin1, 2</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR2</td><td colspan="2">ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic3</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted
• If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and may continue subject in the study</td><td colspan="2">• Viral hepatitis serology[4]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 24hrs after last dose[5]
• 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</td></tr>
</table>

for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high-performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week • 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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. 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.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

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

12.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

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

12.4. Appendix 4: Genetic Research

Genetic Research Objectives and Analyses

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

- Response to medicine, including GSK2838232/RTV 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 or 2 ml saliva sample will be taken for Deoxyribonucleic acid (DNA) extraction. A 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/saliva 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/saliva 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/saliva 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.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the

investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.5.2. 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:

c. Results in death

d. 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.

e. 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.

f. 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

g. Is a congenital anomaly/birth defect

h. 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

i. 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.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Definition of Cardiovascular Events

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

12.5.4. 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. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by

the scale's developer.

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.5.5. 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.

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.
- By specific request, the investigator is obligated to report any grade 2 or higher "alteration in personality-behavior or in mood" or "altered mental status" adverse events that occur in subjects taking this drug, to GSK within 3 days.
- 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.

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data

on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.

- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF

- Facsim0ile 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.

SAE reporting to GSK via PIMS

- Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the Medical Monitor or protocol contact:
  - SAE listing
  - Demographic listing
  - Study treatment listing
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
- If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the Medical Monitor or protocol contact. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.6. Appendix 6: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 24hrs 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 discontinue study medication and be withdrawn from the study
- This will only be included if either of the following apply:
- 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 report the event and submit it to GSK within 24hrs 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.

12.7. Appendix 7: Country Specific Requirements

No country-specific requirements exist.

12.8. Appendix 8: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events Version 1.0, December 2004; Clarification August 2009

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
DERMATOLOGIC				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE AND METABOLIC				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ *1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia **Report only one and specify location**	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< *30 years of age*	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] ≥ *30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< *30 years of age*	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
NEUROLOGIC				
Acute Central nervous system (CNS) Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay < *18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures *New Onset Seizure* ≥ *18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< *18 years of age* *(includes new or pre-existing febrile seizures)*	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA
PREGNANCY, PUERPERIUM, AND PERINATAL				
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	World Health Organization (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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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 < Lower limit of normal (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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 Estimated glomerular filtration rate (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*
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Low Density Lipoprotein (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*
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY				
Absolute cluster of differentiation 4 (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

1. Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
2. As per Bazett's formula.
3. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
4. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.
6. Bone mineral density (BMD) t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.
7. Definition: A delivery of a live-born neonate occurring at ≥20 to <37 weeks gestational age.
8. Definition: A clinically recognized pregnancy occurring at <20 weeks gestational age.
9. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
11. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12. WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.
13. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
14. Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as Grade 2, if <10% of the total bilirubin.
15. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
16. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
17. Male and female sexes are defined as sex at birth.
18. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

12.9. Appendix 9: 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:

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

7. peripheral blood smear
8. indirect bilirubin (abnormal if increased > 50% from baseline)
9. haptoglobin (abnormal if ≤ 25 mg/dL)
10. 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:

11. peripheral blood smear
12. indirect bilirubin
13. haptoglobin
14. 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 9.

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:

15. Temperature > 38.5°C
16. Lymphadenopathy
17. Pharyngitis
18. 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 10.5.

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:

19. Temperature > 38.5°C
20. Lymphadenopathy
21. Pharyngitis
22. 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 10.5.

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 10.5.

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 24 hours via phone or fax. The subject should be closely followed everyday until resolution of the reaction. The subject should remain on the study to be followed for safety and PK as outlined in Section 10.5.

ALLERGIC REACTION

Grade 1 allergic reaction (Pruritis 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:

23. Temperature > 38.5°C
24. Eosinophilia
25. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
26. 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.

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:

27. Temperature > 38.5°C
28. Eosinophilia
29. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
30. 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.

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