TITLE PAGE

Protocol Title: A Two Part Study to Assess i) the Relative Bioavailability and Food Effect of a Novel Tablet Formulation of Boosted-GSK2838232 Compared to Capsule and ii) the Safety and Pharmacokinetics of Repeated Once-Daily Doses of Non boosted GSK2838232

Protocol Number: 205820

Short Title: A two-part study to i) compare a tablet and capsule formulation of GSK2838232 with and without food, and ii) assess the safety and pharmacokinetics of repeated once-daily doses of GSK2838232 without ritonavir.

Compound Number: GSK2838232

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	18-JUL-2017
Original Protocol	09-JUN-2017

Amendment 1 18-July-2017

Overall Rationale for the Amendment: The protocol was amended to include an assessment of neuropsychiatic adverse events at each AE enquiry as well as a statement to inform FDA of any grade 2 or higher alteration in personality-behavior or in mood or altered mental status within 7 days, per FDA request.

Minor typographical errors were also amended in the Schedule of Assessments, the Exclusion Criteria and the Study Assessment and Procedures.

Section # and Name	Description of Change	Brief Rationale
2. SCHEDULE OF ASSESSMENTS	A footnote was added to Table 2 and Table 3 to allow assessment of neuropsychiatric adverse events. The "X" in the column for AE collection in the screening period for Part 2 was deleted.	This change was made per FDA request. Typographical error
6.2. Exclusion Criteria	PR Interval range was corrected.	Typographical error
9.2.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	A sentence was added to indicate sponsor's plan to inform FDA within 7 days of grade 2 or higher alteration in personality-behavior or mental status. AEs collection time was changed to from the start of treatment.	This change was made per FDA request. Typographical error

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1. SYNOPSIS

Protocol Title: A Two Part Study to Assess the Relative Bioavailability and Food Effect of a Novel Tablet Formulation of Boosted-GSK2838232 Compared to Capsule as well as the Safety and Pharmacokinetics of Repeated Once-Daily Doses of Non-boosted GSK2838232

Short Title: A two-part study to i) compare a tablet and capsule formulation of GSK2838232 with and without food, and ii) assess the safety and pharmacokinetics of repeated once-daily doses of GSK2838232 without ritonavir.

Rationale:

This will be a two-part study design that will confirm the acceptability of a tablet formulation in healthy participants for future clinical development of GSK2838232.

Part 1 is a relative bioavailability study that will assess single ritonavir (RTV)-boosted doses of a novel tablet formulation given with food (normal, approximately 30% fat) against the reference capsule formulation also given with food (Part 1A) and then will assess the impact of fasted conditions on the tablet performance (Part 1B).

Part 2 is a study of non-boosted GSK2838232, given as once-daily tablet doses for 11 days in a separate cohort of participants, assuming the tablet performance is considered acceptable from Part 1A. The dose of GSK2838232 used in Part 2 will be confirmed after Part 1A but is likely to be, and will not exceed, 500 mg once daily (QD) as tablets.

Objectives and Endpoints:

Part 1:

Objectives	**Endpoints**
Primary	
• To assess the relative bioavailability of a novel GSK2838232 tablet formulations versus the capsule formulation (Part 1A)	• AUC(0-∞) and Cmax
• To assess the effect of food on GSK2838232 exposure of the tablet formulation (Part 1A and Part 1B)	• AUC(0-∞), Cmax, and tmax

Objectives	Endpoints
Secondary	
• To investigate the safety and tolerability of GSK2838232 following single dose administration as tablets or capsules, with RTV	• GSK2838232 safety parameters: adverse events; absolute values and changes over time of clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), vital signs, and 12-lead electrocardiogram (ECG) parameters from pre-dose values
• To characterize the pharmacokinetics of GSK2838232 after administration of a novel tablet formulation and capsule formulation with food, and the tablet formulation given without food	• tlag, tmax, t½, tlast, C24, and AUC(0-t)

Part 2:

Objectives	Endpoints
Primary	
• To assess the safety of GSK2838232 administered as non-boosted once-daily doses of a tablet formulation for 11 days	• GSK2838232 safety parameters: adverse events; absolute values and changes over time of clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), vital signs, and ECG parameters from pre-dose values
• To assess the pharmacokinetics of GSK2838232 administered as non-boosted once-daily doses of a tablet formulation for 11 days	• Day 1 dose: AUC(0-τ), Cmax, Cτ, tmax, tlag • Day 11 dose: AUC(0-τ), AUC(0-∞), Cmax, Cτ, tmax, t½, tlast
Secondary	
• To assess time to steady-state of GSK2838232 when administered as non-boosted once-daily doses of a tablet formulation for 11 days	• Pre-dose concentrations on Days 2 to 11
• To assess accumulation of GSK2838232 when administered as non-boosted once-daily doses of a tablet formulation for 11 days	• Accumulation ratios: Ro[AUC(0-τ)], R(Cmax), R(Cτ)

AUC(0-τ) = Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state); AUC(0-inf)= Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; Cmax= Maximum observed concentration; t1/2= Apparent terminal phase half-life; tmax= Time of occurrence of Cmax; tlag= Lag-time (time delay between drug administration and first observed concentration above LOQ in plasma); AUC (0-t) = Area under the concentration-time curve from zero up to a definite time t

Overall Design

Part 1:

Part 1 is a relative bioavailability study that will further subdivide into two parts (Part 1A and Part 1B) (Table 1). In Part 1A, the safety and pharmacokinetics (PK) of a novel tablet formulation of GSK2838232 will be evaluated in open label, randomized, cross-over fashion against the capsule formulation as reference. Each actual treatment dose will be separated by a minimum 10-day washout period. Part 1A will be studied in the fed state using a normal fat (i.e., approximately 30%) meal in all participants. In Part 1B, the tablet will be administered in the fasted state to understand the impact of food on relative bioavailability.

Table 1 Treatment Groups in Part 1

Sequence	N	Part 1A		Part 1B
		Period 1	Period 2	Period 3
1	6	A	B	C
2	6	B	A	

1. All treatments in Part 1A to be administered with RTV in a fed state, following two RTV pre-doses.
2. There will be a washout of at least 10 days between each Period.
3. Treatment A = GSK2838232 200 mg/r (as 4 x 50 mg) capsule formulation, fed, normal fat (i.e., approximately 30%) meal (reference).
4. Treatment B = GSK2838232 200 mg/r (as 2 x 100 mg) tablet formulation, fed, normal fat (i.e., approximately 30%) meal.
5. Treatment C = GSK2838232 200 mg/r (as 2 x 100 mg) tablet, confirmed from Part 1A, fasted.

After completion of Part 1A, preliminary PK data will be analyzed, and a decision will be made based on safety, tolerability, relative bioavailability PK criteria, as well as feasibility considerations, as to whether the tablet formulation will be used to conduct Part 1B (fasted) and Part 2.

Part 2:

Part 2 will evaluate non-RTV boosted GSK2838232, given as single daily doses for 11 days in a separate cohort of participants (N=8; 6A/2P). The placebo tablet supplied will not be identical to GSK2838232 and as such will be administered by site staff via an opaque card/paper tube to facilitate the single blind (i.e., the Principal Investigator [PI] and the participants themselves will be blinded as to their treatment). The dose chosen for Part 2 will depend upon the preliminary results of the tablet in Part 1A but is likely to be, but will not exceed, 500 mg (i.e., 5 x 100 mg tablets) QD.

Number of Participants:

It is expected that a sufficient number of participants will be screened in order to enroll approximately 16 healthy participants to provide at least 12 evaluable participants through the three study periods for Part 1 and 10 healthy participants to provide at least 8 evaluable participants for the single study period of Part 2.

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

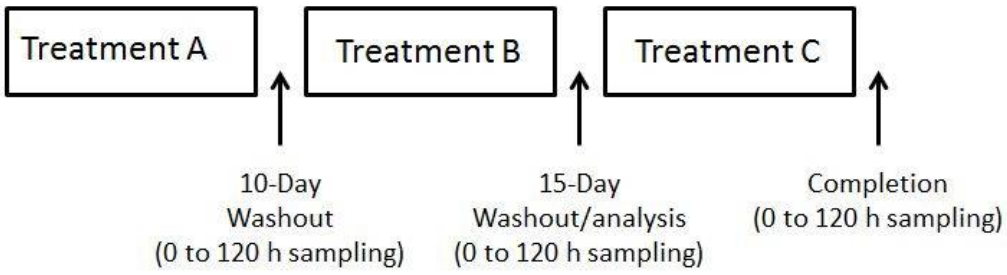
Treatment Groups and Duration:

GSK2838232 as tablets or capsules (at a 200 mg dose level) will be administered with 100 mg RTV, after two pre-doses of 100 mg RTV QD over 48 h. The use of RTV priming is an aspect of GSK2838232 clinical development (specifically relative bioavailability studies) so far and allows a more accurate assessment of what will ultimately happen in the repeat-dose clinical studies with GSK2838232 when administered with RTV. In Part 2 of the study however, GSK2838232 will be administered unboosted and no RTV will be co-administered.

In both Part 1 and Part 2 participants will have a screening visit within 30 days prior to first dose, a minimum 10-day washout period between doses (Part 1 only), and a follow-up visit 7 to 14 days after the last dose. The maximum duration of study participation will be approximately 9 to 10 weeks for Part 1 and 8 to 9 weeks for Part 2.

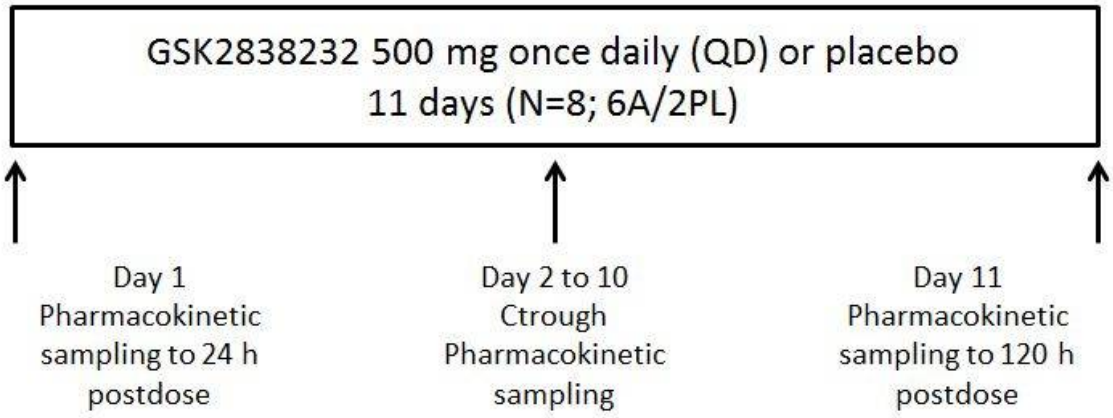
Study Schematic

Part 1



Treatments A and B will be Capsule and Tablet administered in a randomized crossover design with 100 mg Ritonavir with food (fed state) (Part 1A).
Treatment C will be Tablet assessed in Part 1A, administered with 100 mg Ritonavir without food (fasted state) (Part 1B)

Part 2



2. SCHEDULE OF ASSESSMENTS

Please see Table 2 and Table 3 below for the Schedule of assessments for study Parts 1 and 2 respectively.

Table 2 Schedule of Assessments for Part 1A and Part 1B: Single Dose RBA ± Food

Procedure	**Screening** (within 30 days of Day 1 - carried out over multiple days – except as noted in footnotes)	**Periods 1 through 3**										**Follow-up[1]**
		Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**7-14 days**
						24 h	**48 h**	**72 h**	**96 h**	**120 h**		
Admission to Unit		X[2]										
Outpatient Visit	X											X
Informed Consent	X											
Medical/medication/ drug/alcohol history (Demographics)	X											
Full Physical Examination	X											
Brief Physical Examination			X				X					X
Height, Weight, BMI	X											
Inclusion/Exclusion	X											
Vital signs[3]	X		X	X	X	X	X	X				X
12 Lead ECG[4]	X		X	X	X	X	X					X
Echocardiogram[5]	X											
Drug/alcohol/cotinine screen	X	X										
HbsAg, HCV, HIV tests	X											
Hem/Chem/Urine tests[6]	X		X	X		X		X				X
Serum FSH (as appropriate)	X											
Troponin I[7]	X			X	X	X		X				
24 h Holter Monitoring[8]	X											
Pregnancy test (women)	X	X										X
Run-in Dosing with RTV			X	X								
Dosing with GSK2838232+RTV					X							
PK Sampling[9]					X	X	X	X	X	X		
Adverse Event Review[10]				X	X	X	X	X	X	X	X	X
Con Med Review			X	X	X	X	X	X	X	X	X	X
Discharge from Unit[11]						X						
Out Patient Visit							X	X	X	X	X	

BMI = Body Mass Index; ECG = Electrocardiogram; FSH = Follicle Stimulating; HbsAg = Hepatitis B surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; Hem/Chem = Hematology/Clinical Chemistry; RTV = Ritonavir; PK = Pharmacokinetic(s); Con Med = Concomitant medications.

1. Follow-up Visit to take place after Treatment Period 2.
2. When participants stay in the unit across treatment periods, drug/alcohol/cotinine screen and pregnancy test (women) are not required on Day -3 for later periods.
3. On Day 1, Blood pressure (BP) and Heart rate (HR) will be collected at pre-dose (triplicate) and single assessments at 1, 2, 4, 6, 8, 12, 24, 48, and 72 h post-dose.
4. On Day 1, 12-lead ECG will be collected at pre-dose (triplicate), and single assessments at 1, 2, 4, 6, 8, 12, 24, 48 and 72 h post-dose.
5. Echocardiograms must be within 100 days of Day 1.
6. Samples for Chemistry and Hematology: Blood samples will be obtained after an 8-hour fast.
7. Collect one troponin sample to be analyzed at local laboratory. A second sample will be collected, frozen and stored on site for potential high sensitivity troponin analysis.
8. 24-h Holter monitoring to be performed after confirming negative urine drug screen at screening, and must be within 30 days of Day 1. Holter monitoring on other days only if needed.
9. Plasma PK samples for bioanalysis for GSK2838232 will be collected pre-dose (within 15 minutes prior to dosing) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 h post-dose. Samples will be acidified with an equal volume of 50 mmol citrate acid buffer pH 4.0.
10. An AE enquiry will be made at each visit, participants will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status. (see guidance for grading Altered Mental Status in Appendix 4).
11. Participants may be discharged after all study procedures are completed. Participants will be in house for PK blood samples on Day 3 (48 h), Day 4 (72 h), Day 5 (96 h) and Day 6 (120 h) of both study periods.

Table 3 Schedule of Assessments for Part 2: Repeated Doses for 11 days:

Measurement	**Screening** (within 30 days of Day 1 - carried out over multiple days - except as noted in footnotes)	**Day –1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11 0 h**	**Day 12 24 h**	**Day 13 48 h**	**Day 14 72 h**	**Day 15 96 h**	**Day 16 120 h**	**Follow-up 7-14 days after last dose**
Admission to Unit		X																	
Informed Consent	X																		
Medical/medication/ drug/alcohol history (Demographics)	X																		
Full Physical Examination	X													X					
Brief Physical Examination		X																	X
Height, Weight, BMI	X																		
Inclusion/Exclusion	X																		
Medical History	X																		
Vital Signs[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
12-lead ECG[2]	X	X	X	X	X		X			X			X	X					X
Echocardiogram[3]	X																		
Drug/alcohol/ /cotinine Screen	X	X																	
HbsAg, HCV, HIV Testing	X																		
Hem/Chem tests[4]	X	X		X		X		X		X			X			X			X
Urinalysis	X	X		X		X							X			X			X
Serum FSH (as appropriate)	X																		
Troponin I[5]	X	X	X	X			X			X			X			X			

Measurement	**Screening** (within 30 days of Day 1 - carried out over multiple days - except as noted in footnotes)	**Day –1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11 0 h**	**Day 12 24 h**	**Day 13 48 h**	**Day 14 72 h**	**Day 15 96 h**	**Day 16 120 h**	**Follow-up 7-14 days after last dose**
24 h Holter Monitoring[6]	X																		
Pregnancy Test (females)	X	X																	X
Dosing of GSK2838232			X	X	X	X	X	X	X	X	X	X	X						
Plasma PK sampling[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Assessment[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge from Unit															X[9]				
Out Patient Visit	X															X	X	X	X

BMI = Body Mass Index; ECG = Electrocardiogram; FSH = Follicle Stimulating Hormone; HbsAg = Hepatitis B surface Antigen; HCV = Hepatitis C Virus; Hem/Chem = Hematology/Clinical Chemistry; HIV = Human Immunodeficiency Virus; IP = Investigational Product; PK = Pharmacokinetic(s).

1. A single blood pressure (BP) and Heart rate (HR) assessment will be collected at screening and Day -1. On Day 1 triplicate BP and HR will be collected at pre-dose and single assessments at 1, 4, 24, 48 and 72 h (Day 4) post-dose, Day 5, Day 6, Day 7, Day 8, Day 9, Day 10, Day 11 at pre-dose (triplicate), and single assessment at 1, 4, 24, 48 and 72 h post-dose, and at follow-up.
2. A single 12-Lead ECG will be collected at screening and Day -1. On Day 1 triplicate 12-Lead ECGs will be collected at pre-dose, and then single 12-Lead ECGs at 1, 4 and 12 h post-dose. Single 12-Lead ECGs will be collected on Days 2, 3, 5, 8. On Day 11 triplicate 12-Lead ECGs will be collected pre-dose, and then single 12-Lead ECGs collected at 1, 4, 12 and 24 h post-dose and at follow-up.
3. Echocardiograms must be within 100 days of Day 1.
4. Samples for Chemistry and Hematology: Blood samples will be obtained after an 8-hour fast.
5. Collect one troponin sample to be analyzed at local laboratory. A second sample will be collected and frozen for potential high sensitivity troponin analysis.
6. 24-h Holter monitoring to be performed after confirming negative urine drug screen at screening, and must be within 30 days of Day 1. Holter monitoring on other days only if needed.

7. Plasma PK samples for GSK2838232 will be collected as follows: Day 1; pre-dose (within 15 minutes prior to dosing) and 0.5,1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 h post-dose (prior to Day 2 dose). Days 3 to 10 pre-dose (within 15 minutes prior to dosing). Day 11; pre-dose (within 15 minutes prior to dosing) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 120 h post-dose. Samples will be acidified with an equal volume of 50 mmol citrate acid buffer pH 4.0.
8. An AE enquiry will be made at each visit, participants will be asked if they have experienced any neuropsychiatric adverse events, including psychosis or altered mental status. (see guidance for grading Altered Mental Status in Appendix 4).
9. Participants will be discharged after all study procedures are completed on the morning of Day 13 (after the 48 h post-final dose sample time point) with instructions to return fasted on the mornings of Day 14 for 72 h PK sample, Day 15 for 96 h PK sample, and Day 16 for 120 h PK sample.

3. INTRODUCTION

3.1. Study Rationale

This will be a two-part study design that will confirm the acceptability/selection of a tablet formulation for future clinical development of GSK2838232.

Part 1 is a relative bioavailability study that will assess single RTV-boosted doses of a novel tablet formulation given with food (normal, approximately 30% fat) against the reference capsule formulation also given with food (Part 1A) and then will assess the impact of fasted conditions on the tablet performance (Part 1B).

Part 2 is a study of non-boosted GSK2838232, given as once-daily tablet doses for 11 days in a separate cohort of participants, assuming the tablet performance is considered acceptable from Part 1A. The dose of GSK2838232 used in Part 2 will be confirmed after Part 1A but is likely to be, and will not exceed, 500 mg QD as tablets.

3.2. Background

Human immunodeficiency virus (HIV) infection affects approximately 37 million people worldwide [UNAIDS Fact Sheet, 2015]. While antiretroviral (ARV) therapy has been tremendously successful over the past 20 years in reducing morbidity and mortality, there continues to be a medical need given viral resistance to existing drug classes and acute and chronic drug toxicities. New drug classes targeting novel viral replication mechanisms would overcome HIV resistance to existing ARV drugs and may improve long-term safety by replacing older agents with known safety liabilities.

Maturation inhibitors represent a new class of compound for the treatment of HIV infection, distinct from viral entry, protease, reverse transcriptase or integrase inhibitors [Qian, 2009]. GSK2838232 is a maturation inhibitor being developed for the treatment of human HIV-1.

An extensive preclinical package of work has been completed, including biology/ virology, safety assessment (toxicology), and preclinical PK studies. GSK2838232 has also been administered to 124 healthy non-HIV-infected human participants in four clinical studies completed so far across a number of single and repeated dose designs, utilizing early clinical formulations. The PK, safety, and tolerability profile obtained so far supports continued clinical development of GSK2838232, and there is an ongoing study in HIV-infected patients that was initiated in the United States (US) in 1Q2017. There is a need to transition to a more suitable tablet formulation, which is one of the major objectives of this study.

3.2.1. Pharmacokinetic Summary

The original formulation used in the first three studies with GSK2838232 (HMI116787, 200207, and 200912) was Spray Dried Dispersion (SDD). Data from Study 200912 demonstrated that a change to the active pharmaceutical ingredient (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.

- 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 powder in bottle (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 to 50% of the bioavailability of SDD formulation, but there was a large observed range of relative intra-subject exposures (11 to 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 to 18 hours to 34 to 42 hours in the presence of steady-state RTV, regardless of formulation.

- After single doses of 50 mg to 250 mg GSK2838232 with RTV, increases in maximum observed concentration (Cmax) and area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC[0-∞]) values were broadly proportional to the increase in dose. On Day 11 after repeated daily 20 mg to 200 mg doses of GSK2838232 with RTV, increases in Cmax and area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state) (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% to 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.

Variability remains fairly constant across formulations and boosted versus unboosted at around 30% to 40% (moderate-high).

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

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2838232 may be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

3.3.1. 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 four 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. Toxicology studies in rat and dog (3, 6 and 9 months) 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	Participants 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 ECG 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 PK stopping criteria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	clinically significant abnormality in electrocardiogram (ECG) values other than the two serious adverse events (SAEs) documented and discussed. Review of published bevirimat preclinical and clinical safety data indicates no significant toxicities or adverse events (AEs) of interest, other than a 30% incidence of gastrointestinal symptoms (including diarrhea). There were no significant cardiovascular AEs reported in published clinical studies.	
Hepatic	In dogs given 70 mg/kg/day for 9 months, there were reversible liver changes consisting of pigment accumulation (presumed bile) associated in some individuals with modest inflammatory cell infiltration and isolated serum alanine aminotransferase activity (ALT) elevations. Adverse effects in the liver were limited to one species and manifested only after prolonged dosing with no apparent effect on the clinical health of the animals; the effects were of modest severity and reversible, and the potential for such effects in human participants can be monitored in clinical studies. In study 200912, a 47-year-old female who received a dose of GSK2838232 20 mg and 9 days of RTV 100 mg, developed abdominal pain, nausea, flatulence with grade 4 elevations in ALT/ aspartate aminotransferase (AST) and grade 2 elevations in total bilirubin. A liver ultrasound revealed a dilated	Persons with underlying liver or biliary disease or abnormalities in liver function tests will be excluded from study participation. Participants will be closely monitored for symptoms and signs of liver dysfunction, including serial monitoring of liver enzymes and chemistries. Use of concomitant medications/supplements and intake of alcohol is not allowed during the study. Exposures of GSK2838232 will be closely monitored in the clinical study so as to not exceed PK stopping criteria. The study has pre-defined liver stopping criteria.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	common bile duct and gallstones. An endoscopic retrograde cholangio-pancreatography (ERCP) showed a dilated common bile duct with no filling defect. She was diagnosed with a common bile duct obstruction due to gallstones that spontaneously resolved. The Investigator considered this liver event as unrelated to study drug.	
Ritonavir (RTV)		
General	The most frequently reported adverse drug reactions among patients receiving RTV were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain [upper and lower]), neurological disturbances (including paresthesia and oral paresthesia), rash, and fatigue/asthenia.	Participants will be closely monitored for any symptoms potentially associated with RTV administration.
Cardiovascular	The RTV label includes the following cardiovascular AEs (which occurred in less than 2% of adult patients receiving RTV in all phase II/phase III studies and considered at least possibly related or of unknown relationship to treatment and of at least moderate intensity): cardiovascular disorder, cerebral ischemia, cerebral venous thrombosis, hypertension, hypotension, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis, postural hypotension, tachycardia and vasospasm. During post-marketing use of RTV first-degree AV block, second-degree AV block, third-degree AV block, right	Participants will be closely monitored for any symptoms potentially associated with RTV administration. Specifically, participants will be clinically monitored for any signs of myocardial injury (chest pain, shortness of breath, pain with inspiration, cardiac troponin I [cTnI], ECG changes), elevated heart rate or arrhythmias. Serial ECGs will be used at each treatment period on-study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	bundle branch block have been reported.	
Hepatitis	Hepatic transaminase elevations > 5 x the upper limit of normal, clinical hepatitis, jaundice, and hepatic dysfunction (including fatalities) have occurred in patients receiving RTV alone or in combination with other antiretroviral drugs. There may be an increased risk for transaminase elevations in patients with underlying hepatitis, pre-existing liver diseases, or liver enzyme abnormalities, and in patients taking multiple concomitant medications and/or with advanced acquired immunodeficiency syndrome (AIDS).	Enrolment into the study will be limited to healthy volunteers who do not have not underlying liver disease, hepatitis or liver enzyme abnormalities. Liver enzymes (ALT, AST, total and direct bilirubin, alkaline phosphatase) will be determined at screening and monitored throughout the study period.
Pancreatitis	Pancreatitis has been observed in patients receiving RTV therapy, and in some cases fatalities have been observed.	Participants will be closely monitored for any symptoms of pancreatitis, including nausea, vomiting, abdominal pain and anorexia. Lipase will be monitored throughout the treatment period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Adverse Drug Reactions due to Drug Interactions	Initiation of RTV, a cytochrome P (CYP) 3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving RTV, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of RTV, respectively. These interactions may lead to clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications, or clinically significant adverse reactions from greater exposures of RTV	Use of concomitant medications (besides GSK2838232), herbals and dietary supplements is exclusionary and will be prohibited. Participants will also be instructed to avoid ingestion of grapefruit juice.

3.3.2. Benefit Assessment

This is a study in healthy participants and as such there is no expected benefit to the participants that will receive GSK2838232. Participation in this study may contribute to the process of developing new therapies for HIV. There may be benefit to individual participants from the medical evaluations and assessments that could identify conditions to which the participant was previously unaware.

3.3.3. Overall Benefit: Risk Conclusion

GSK2838232, with its novel mechanism of action, can potentially provide benefit to HIV-1 infected patients experiencing virologic failure due to multi-drug resistant virus or those with intolerance to other antiretroviral therapies. Given the preclinical profile and the clinical profile to date, the overall risk to healthy participants at the proposed GSK2838232 doses (with or without RTV) is predicted to be low.

While cardiovascular-related events have been observed, the totality of the pre-clinical and clinical data suggest a low likelihood of cardiac toxicity from GSK2838232. Nevertheless, there will be close monitoring of cardiovascular (CV) parameters, as described below, and CV-related study stopping criteria will be implemented to further reduce the potential risk to participants.

In addition, the 9-month dog toxicity study identified adverse liver findings that were mild, reversible, can be monitored, and only occurred after prolonged exposure to concentrations that are greater than the average exposure expected from the highest dose level in this study. To diminish the potential risk of liver toxicity, persons with underlying hepatic or biliary abnormalities will be excluded, liver enzymes will be closely monitored, and liver-stopping criteria will be implemented in this study.

Participants will also be at risk for AEs from RTV use (Part 1 only) and will be monitored closely for such events.

Projected exposure and Ctrough values for the proposed doses of GSK2838232 indicate a high likelihood of attaining concentrations that will afford significant anti-viral benefit to HIV-infected patients but will be below the no AE dose level (NOAEL) seen in preclinical studies. Therefore, the risks in this study are considered justified based on benefits that may be afforded to participants with HIV infection.

4. OBJECTIVES AND ENDPOINTS

Part 1:

Objectives	Endpoints
Primary	
• To assess the relative bioavailability of a novel GSK2838232 tablet formulations versus the capsule formulation (Part 1A)	• AUC(0-∞) and Cmax,
• To assess the effect of food on GSK2838232 exposure of the tablet formulation (Part 1A and Part 1B)	• AUC(0-∞), Cmax, and tmax
Secondary	
• To investigate the safety and tolerability of GSK2838232 following single dose administration as tablets or capsules, with RTV	• GSK2838232 safety parameters: AEs; absolute values and changes over time of clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), vital signs, and ECG parameters from pre-dose values
• To characterize the PK of GSK2838232 after administration of a novel tablet formulation and capsule formulation with food, and the tablet formulation given without food	• tlag, tmax, t½, tlast, C24, and AUC(0-t)

Part 2:

Objectives	Endpoints
Primary	
• To assess the safety of GSK2838232 administered as non-boosted once-daily doses of a tablet formulation for 11 days	• GSK2838232 safety parameters: AEs; absolute values and changes over time of clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), vital signs, and ECG parameters from pre-dose values
• To assess the PK of GSK2838232 administered as non-boosted once-daily doses of a tablet formulation for 11 days	• Day 1 dose: AUC(0-τ), Cmax, Cτ, tmax, tlag • Day 11 dose: AUC(0-τ), AUC(0-∞), Cmax, Cτ, tmax, t½, tlast

Objectives	Endpoints
Secondary	
• To assess time to steady-state of GSK2838232 when administered as non-boosted once-daily doses of a tablet formulation for 11 days	• Pre-dose concentrations on Days 2 to 11
• To assess accumulation of GSK2838232 when administered as non-boosted once-daily doses of a tablet formulation for 11 days	• Accumulation ratios: Ro[AUC(0-τ)], R(Cmax), R(Cτ)

t1/2= Apparent terminal phase half-life; tmax= Time of occurrence of Cmax; tlag= Lag-time (time delay between drug administration and first observed concentration above LOQ in plasma); AUC (0-t) = Area under the concentration-time curve from zero up to a definite time t

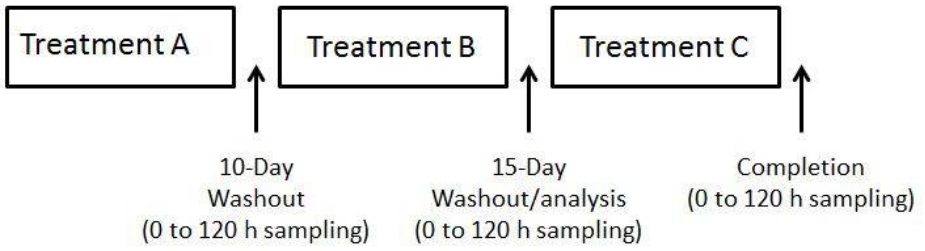
5. STUDY DESIGN

5.1. Overall Design

This study is divided into two study parts, Part 1 (Figure 1) and Part 2 (Figure 2).

Part 1:

Figure 1 Part 1: Single Dose, Food Effect Study Design Schematic



Treatments A and B will be Capsule and Tablet administered in a randomized crossover design with 100 mg Ritonavir with food (fed state) (Part 1A).
Treatment C will be Tablet assessed in Part 1A, administered with 100 mg Ritonavir without food (fasted state) (Part 1B)

- Part 1 is a relative bioavailability study (Table 4) that will further subdivide into two parts (Part 1A and Part 1B).
- In Part 1A, the safety and PK of a novel tablet formulation of GSK2838232 will be evaluated in open label, randomized, cross-over fashion against the capsule formulation as reference.

- Each actual treatment dose will be separated by a minimum 10-day washout period. Part 1A will be studied in the fed state using a normal fat (i.e., approximately 30%) meal in all participants.
- The safety and PK will be evaluated, and the tablet will be evaluated for suitability, and further clinical assessment in Part 1B, where the tablet will be administered in the fasted state to understand the impact of food on relative bioavailability.
- GSK2838232 as tablets or capsules (at a 200 mg dose level) will be administered with 100 mg RTV, after two pre-doses of 100 mg RTV QD over 48 h. The use of RTV priming is an aspect of GSK2838232 clinical development (specifically relative bioavailability studies) so far and allows a more accurate assessment of what will ultimately happen in the repeat-dose clinical studies with GSK2838232 when boosted with RTV. In Part 2 of the study, however, GSK2838232 will be administered unboosted and no RTV will be co administered.
- Participants will have a screening visit within 30 days prior to first dose, a minimum 10-day washout period between doses, and a follow-up visit 7 to 14 days after the last dose. The maximum duration of study participation will be approximately 9 to 10 weeks.

Table 4 Study Design for Part 1

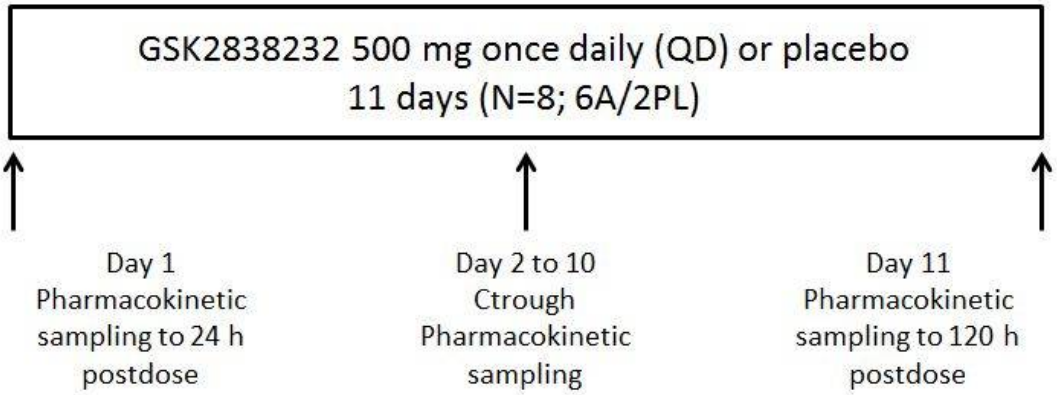
Sequence	N	Part 1A		Part 1B
		Period 1	Period 2	Period 3
1	6	A	B	C
2	6	B	A	

1. All treatments in Part 1A to be administered with RTV in fed state, following two RTV pre-doses.
2. There will be a washout of at least 10 days between each Period.
3. Treatment A = GSK2838232 200 mg/r (as 4 x 50 mg) capsule formulation, fed, normal fat (i.e., approximately 30%) meal (reference).
4. Treatment B = GSK2838232 200 mg/r (as 2 x 100 mg) tablet formulation, fed, normal fat (i.e., approximately 30%) meal.
5. Treatment C = GSK2838232 200 mg/r (as 2 x 100 mg) tablet, confirmed from Part 1A, fasted.

After completion of Part 1A, preliminary PK data will be analyzed, and a decision will be made based on tolerability, relative bioavailability PK criteria, as well as feasibility considerations, as to whether the tablet formulation will be used to conduct Part 1B (fasted) and Part 2.

Part 2:

Figure 2 Single Daily Dose Study Design Schematic



- Part 2 will evaluate non-RTV boosted GSK2838232, given as single daily doses for 11 days in a separate cohort of participants (N=8; 6A/2P).
- The placebo tablet supplied will not be identical to GSK2838232 and as such will be administered by site staff via an opaque card/paper tube to facilitate the single blind (i.e., the Principal Investigator [PI] and the participants themselves will be blinded as to their treatment).
- The dose chosen for Part 2 will depend upon the preliminary results of the tablet in Part 1A but is likely to be, but will not exceed, 500 mg (i.e., 5 x 100 mg tablets) QD.
- Participants will have a screening visit within 30 days prior to first dose, and a follow-up visit 7 to 14 days after the last dose. The maximum duration of study participation will be approximately 8 to 9 weeks.

Study Population:

The study population will consist of healthy male or female participants (women of child bearing potential [WOCBP] are permitted as long as the criteria for contraception are adhered to), as per inclusion/exclusion criteria (Section 6).

Note: Participants in both Part 1 and Part 2 will have a 24-h Holter screen as part of baseline evaluation. Holter monitoring may apply during the study period if needed.

Study Plan:

Because of the requirement to begin RTV pre-dosing 48 hours before each treatment dose in Parts 1A and 1B, participants will be admitted to the Clinical Unit three nights before each of the treatment periods and remain in the Unit until the last (120 h) PK time-point of each treatment period is collected. There is no such early admission requirement for Part 2 (non-boosted GSK2838232).

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

5.2. Number of Participants

In order to have sufficient evaluable participants for the above mentioned study objectives, it is expected that a sufficient number of participants will be screened in order to enroll a sufficient number of participants for analysis as given below:

Part 1:

It is expected that approximately 16 healthy participants will be enrolled to provide at least 12 evaluable participants through the three study periods (at least 6 participants per treatment). Participants will be evenly assigned to one of the two treatment sequences for the crossover design Part 1A.

Part 2:

It is expected that 10 healthy participants will be enrolled to provide at least 8 evaluable participants through the single study period.

5.3. Participant and Study Completion

A completed participant is one who has received the study treatment per the protocol and who has completed all phases of the study including the follow-up visit.

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

5.4. Scientific Rationale for Study Design

Study **HMI116787** was the First Time in Human (FTiH) clinical trial of GSK2838232 and assessed the safety and tolerability of escalating doses (5 mg to 100 mg), food effect and the impact of steady-state RTV on GSK2838232 PK. The study was completed in November 2013, and safety and PK data warranted continued investigation of GSK2838232.

Subsequent clinical studies 200912 and 200207 were carried out in healthy participants and extended the dose range studied as follows:

- Study **200207**: Repeated doses of GSK2838232 SDD alone (20 mg and then 50 mg QD for 8 days), and then with RTV as 10 mg SDD GSK2838232 + RTV QD for 5 days.
- Study **200912**: Dosed up to 200 mg GSK2838232 alone as single doses (as either SDD or API PiB) or 20 mg GSK2838232 API PiB single dose with steady-state RTV.

Study **204953** has completed the clinical phase in 4Q2016 and was a double-blind (except for the relative bioavailability cohort, Part 1B), placebo-controlled, single

(Part 1A; dose levels of 50 to 250 mg) followed by a repeat dose (Part 2; dose levels of 20 to 200 mg QD) escalation study to investigate the safety, tolerability and PK of GSK2838232 as API, co-dosed with RTV 100 mg QD. GSK2838232 was administered without RTV in the last cohort of repeat dosing to assess achievable plasma concentrations with unboosted GSK2838232 (200 mg twice daily [BID]).

This study then completes the assessment of clinical trial formulation (tablets) for Phase IIb and III as well as an assessment of higher QD doses of GSK2838232 unboosted.

5.5. Dose Justification

The dose for Part 1A and Part 1B of this study will be 200 mg (achieved as either 4 x 50 mg capsules or 2 x 100 mg tablets) administered with 100 mg RTV. This dose level was tested in Study 204953 and provides a suitable PK profile for assessment of formulation performance.

The dose for Part 2 will be confirmed from Part 1A but is likely to be, and will not exceed, 500 mg (as 5 x 100 mg tablets). The dose of 500 mg is justified on the grounds that the utility of non-boosted GSK2838232 in a QD regimen may now be an achievable goal. GSK2838232 has been previously assessed in repeated doses of i) 200 mg GSK2838232 QD in combination with 100 mg RTV QD for 11 days, and ii) non-boosted 200 mg GSK2838232 BID for 11 days (Study 204953). This study will assess the highest practical once-daily dose of GSK2838232.

6. STUDY POPULATION

Specific information regarding warnings, precautions, contraindications, AEs and other pertinent information on the GSK IP or other study treatment that may impact participant eligibility is provided in the IB.

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

6.1. Inclusion Criteria

A participant 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 PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. 3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, and outside the reference range for the population being studied, may be included only if the Investigator in consultation with the Medical Monitor, if required, 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: 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.
WEIGHT
5. Body weight ≥50.0 kg (110 lbs.) for men and ≥45.0 kg (99 lbs) for women and body mass index (BMI) within the range 18.5 to 31.0 kg/m^2 (inclusive).

SEX
6. Males or females A female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test), not lactating, and of non-reproductive potential which is defined as: **Reproductive potential:** There is no definitive drug-drug interaction (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 may only be enrolled if they are using two forms of complementary contraception, which must include at least one barrier method. They will be counselled on safer sex practices.

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 participants 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 Standard operating Procedure (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 participants understand how to properly use these methods of contraception.

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

6.2. Exclusion Criteria

A participant 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 transaminase (ALT) >1.5x upper limit of normal (ULN) 2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities. 4. Participants who have asthma or a history of asthma. 5. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.
CONCOMITANT MEDICATIONS
6. 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 participant safety.
RELEVANT HABITS
7. History of regular alcohol consumption (within 6 months prior to screening or unable to refrain from alcohol use from 5 days prior to admission through the last blood sample collected) defined as: • For US sites: 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.

8. Regular use of tobacco- or nicotine- containing products within 6 months prior to screening. Unable to refrain from smoking from the Screening Visit through the last blood sample collected. As confirmed by a urine cotinine test.

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), or positive hepatitis C virus (HCV) 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 (>0.045ng/ml by the Dimension Vista cTnI assay) for a given assay.

12. A positive pre-study drug/alcohol screen.

13. A positive test for HIV antibody.

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 participant 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. Exclusion Criteria for 24-hour Screening Holter:

    - Any symptomatic arrhythmia (except isolated extra systoles).
    - Sustained cardiac arrhythmias (such as atrial fibrillation or flutter, supraventricular tachycardia (≥ 10 consecutive beats), complete heart block).
    - Non-sustained or sustained ventricular tachycardia (defined as ≥ 3 consecutive ventricular ectopic beats).
    - Any conduction abnormality (including but not specific to left or right incomplete or complete bundle branch block, atrioventricular (AV) block [2nd degree or higher], Wolff Parkinson White (WPW) syndrome etc.).

- Sinus Pauses >3 seconds.
- 300 or more supraventricular ectopic beats in 24 hours.
- 250 or more ventricular ectopic beats in 24 hours.

18. Any clinically significant abnormal echocardiogram finding (should be discussed with the Medical Monitor prior to enrolment).

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

	Males	Females
Heart rate	<45 or >100 bpm	<50 or >100 bpm
PR Interval	<120 or > 220 msec	
QRS duration	<70 or >120 msec	
QTc interval (Fridericia's)	>450 msec	

- *Note: A heart rate from 100 to 110 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 re-polarization).
- 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 Investigator OR GSK Medical monitor, will interfere with the safety for the individual participant.
- Non-sustained or sustained ventricular tachycardia (≥ 3 consecutive ventricular ectopic beats).

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Participants should avoid consumption of red wine, Seville oranges, grapefruit or grapefruit juice (and/or pomelos, exotic citrus fruits, grapefruit hybrids or fruit juices) from 5 days before the first dose of study medication, until follow-up.

Participants should refrain from eating poppy seed-containing food (e.g., poppy cake) at least 3 days before admission as this can falsify the urine drug screen. A positive illicit drug result will lead to exclusion from the remainder of the study.

- Water is allowed ad libitum throughout the study.

- While in residence in the clinical research unit (admission through discharge), participants will be restricted to food and beverage that is site-provided at specific times. Participants are expected to complete all meals and snacks (100%) within 25 minutes (Parts 1A and Part 1B). Non-compliance will be recorded.
- Participants will be fed a "normal" standardized diet consisting of an average between 3400 to 4000 kcal for each full day in residence (with the exception of Part 1B dosing days where dosing is conducted under fasted conditions). A 5% variance in calories is allowed. The macronutrient distributions and caloric criteria are within the recommendations in the *Dietary Guidelines for Americans*, 2010.

- **Part 1A and Part 2**
- Standardized meals will be provided to participants in Part 1A starting with Day 1 through discharge from the clinical research unit.
- Standardized meals and snacks should be completed within 25 minutes. Participants will be expected to complete all meals and snacks (100%). Non-compliance on Day 1 will be recorded in increments of 25% (e.g., 0%, 1-25%, 26-50%, 51-75% or 76-100% meal or snack completed).
- Participants will undergo at least a 10-hour overnight fast then will be provided a meal 30 minutes before dosing and will be expected to complete the meal within 25 minutes. Lunch will be provided approximately 4 hours after morning dosing and dinner will be provided approximately 9 hours after morning dosing. On Day 1, all participants will receive identical meals at breakfast, lunch, dinner and snack. On non-dosing days, meals will be served per the standard times at the clinical research unit.
- **Part 1B (tablet, fasted):**
- Participants will undergo at least a 10-hour overnight fast prior to Part 1B GSK2838232 tablet dosing. On the day of dosing, participants will continue fasting after dosing (no breakfast). Lunch will be provided approximately 4 hours after morning dosing and dinner will be provided approximately 9 hours after morning dosing. On Day 1, all participants will receive identical meals at lunch, dinner and snack. On non-dosing days, meals will be served per the standard times at the clinical research unit.

6.3.2. Caffeine, Alcohol, and Tobacco

- All enrolled participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 48 hours before the start of dosing until collection of the final PK sample during each session.
- All enrolled participants will abstain from red wine for 5 days and other alcohol for 24 hours before the start of dosing until collection of the final PK sample during each session.

- Participants who currently use or have used tobacco products within 6 months of Screening will not be enrolled.
- Participants must refrain from all illicit drugs throughout the study (from Screening until discharge from the study). Drug screening will occur as indicated in the Schedule of Assessments (Table 2 and Table 3) for each Part of the study. Participants should refrain from eating poppy seed-containing food (e.g., poppy cake) at least 3 days before admission as this can falsify the urine drug screen. A positive illicit drug result will lead to exclusion from the remainder of the study.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 1 week before Admission and during the course of the study and refrain from increasing their activity above that which they normally perform. Participants may participate in light recreational activities during studies (e.g., watch television, read).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the PI. Rescreened participants should be assigned the same participant number as for the initial screening.

7. TREATMENTS

The term 'study treatment' is used throughout the protocol to describe GSK2838232, RTV or the combination of the products received by the participant as per the protocol design.

GSK2838232 will be supplied by GSK as prefilled capsules or tablets in bulk for dispensing to participants at the site according to the treatment code.

Ritonavir – commercially available; will be purchased/supplied either by PAREXEL or GSK.

7.1. Treatments Administered

Details of the study treatment are provided in Table 5 below.

Table 5 Investigational Product and Other Study Treatment

Study Treatment Name:	GSK2838232	NORVIR (ritonavir, RTV)	Placebo (Part 2 only)
Dosage formulation:	Tablets or Capsule	Tablets	*Tablet (non-matching) for the GSK2838232 tablet formulation)
Unit dose strength(s)/Dosage level(s):	200 mg: Capsules: 4 x 50 mg Tablets: 2 x 100 mg	100 mg	Not applicable
Route of Administration	Oral	Oral	Oral
Dosing instructions:	Part 1A: To be taken with water and a meal (fed conditions) Part 1B: To be taken with water after a fast (fasted conditions) Part 2: To be taken with water and a meal once daily for 11 consecutive days	Part 1A: To be taken with water and a meal (fed conditions) Part 1B: To be taken with water after a fast (fasted conditions)	Part 2: To be taken with water and a meal once daily for 11 consecutive days
Packaging and Labeling	GSK2838232 will be supplied by GSK as prefilled capsules or tablets in bulk for dispensing to participants at the site according to the treatment code.		Placebo for GSK2838232 tablets will be provided, although are non-matching as tablets
Manufacturer/Source of procurement	GSK	Procured by PAREXEL	GSK
Physical Form	Pink unmarked capsule White to slightly colored tablet.	White film-coated ovaloid tablets	White to slightly colored tablet.

*The placebo (tablet) supplied will not be identical to GSK2838232 and as such will be administered by site staff via an opaque card/paper tube to facilitate the single blind (i.e., the participant will be blinded as to their treatment).

The unblinded pharmacist or qualified designee will prepare GSK2838232 and placebo according to a pre-generated schedule of randomized treatment assignments.

7.1.1. Medical Devices

- Not applicable.

7.2. Dose Modification

Not applicable.

7.3. Method of Treatment Assignment

Participants will be assigned to study treatment in accordance with the computer generated randomization schedule generated by PAREXEL, using SAS version 9.3 or higher. A separate randomization schedule will be generated for each part of the study. At Screening, potential study participants will be assigned a screening number. Participants will be randomized before the first dose of Study Drug in Part 1A (GSK2838232 tablet or capsule, with RTV) or Part 2 (GSK2838232 tablet or placebo tablet, without RTV) after all screening assessments have been completed and after the Investigator has verified that they are eligible per study inclusion/exclusion criteria. No participant may begin treatment before randomization and assignment of a unique participant identification number.

Each participant scheduled to receive study treatment will receive a participant number when randomized. The randomization number will determine the allocation of treatment sequences (ABC or BAC) for Part 1, and of treatment (GSK2838232 without RTV or placebo) for Part 2. Allocation to treatment for Part 1A or Part 1B (with Part 2 being fixed) will be according to a predetermined random order.

7.4. Blinding

Part 1 of the study will be open label and thus not be blinded.

Part 2 of the study will be single blinded because of the unavailability of matching placebo tablets. Certain site personnel preparing the treatment for administration will know what the treatment is but will administer the tablet or tablet placebo via an opaque tube/envelope to the participants. The PI and the participants will be completely blinded to specific participant treatment assignment.

When possible, GSK/ contract research organization (CRO) personnel will not have access to participant-specific treatment assignment so as to not potentially introduce bias in discussions with the study center.

The Investigator or treating physician may unblind a participant's treatment (Part 2 single blind) assignment **only in the case of an emergency** when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant. Whenever possible, the Investigator must first discuss options with the GSK Medical Monitor or appropriate GSK study personnel **before** unblinding the participant's treatment assignment. If this is impractical, the Investigator must notify GSK as soon as possible, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

A participant will be withdrawn if the participant's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the data collection tool.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to Investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of GSK2838232, RTV or placebo will be detailed in a Technical Agreement. The formulations will be extemporaneously prepared as per instructions that will be reviewed and approved by GSK before use.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. 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).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.
5. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the

Investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

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

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

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

Participants must abstain from taking prescription or nonprescription 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) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the Investigator and sponsor, the medication will not interfere with the study.

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

7.8. Treatment after the End of the Study

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

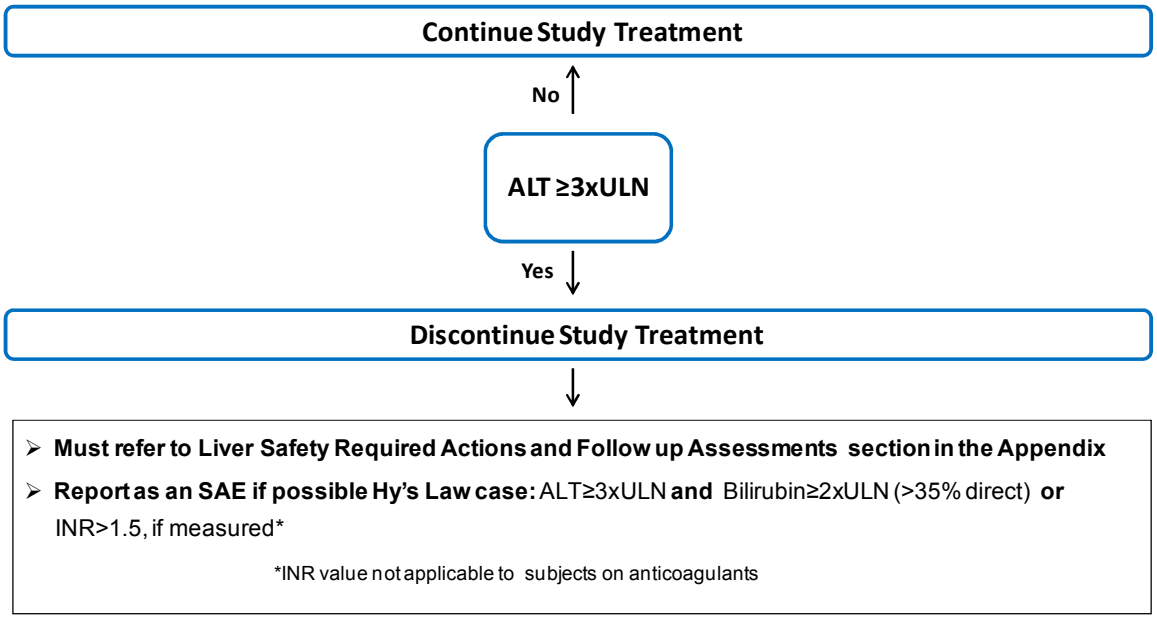
8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

Study treatment will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.3, Appendix 3.

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:

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

Discontinuation of study treatment for abnormal liver tests should be considered by the Investigator when a participant meets one of the conditions outlined in the algorithm above or if the Investigator believes that it is in the best interest of the participant.

8.1.2. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
    - For example, if a participant is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual participant as well.
    - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- A participant that meets the bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment.
    - QTc, QTcB, QTcF >500 msec,
    - Change from baseline: QTcF >60 msec

8.1.3. Temporary Discontinuation

Not applicable.

8.1.4. Rechallenge

Not applicable.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples collected and not tested, and the Investigator must document this in the site study records.
- Refer to the Schedule of Assessments (Table 2 and Table 3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

Each participant will have adequate time to provide informed consent of his or her own free will and before conducting any study procedures according to the International Conference on Harmonization (ICH) and Code of Federal Regulations (CFR) guidelines. Each participant will be provided a copy of the signed informed consent document (ICF) before the initiation of any study procedures.

After a participant has provided written informed consent and within 30 days of the first dose of study treatment, the Investigator or other study personnel will determine if the participant is eligible for enrolment in the study. This will be done by reviewing the inclusion and exclusion criteria and completing all of the screening assessments outlined in the Schedule of assessments Tables (Table 2 and Table 3). Screening assessments may be carried out over more than 1 day provided that all required assessments are completed within 30 days before the first administration of study treatment.

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 Schedule of Assessments Tables (Table 2 and Table 3), are essential and required for study conduct.

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, 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. In the event that the timing for a scheduled assessment conflicts with an

assessment that has to be repeated, the scheduled assessment will be performed on time/as scheduled and the repeat assessments will be conducted when feasible.

The timing and number of planned study assessments, including: safety and PK assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The Institutional Review Board (IRB) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

The timing of planned study assessments is listed in the Schedule of Assessments Tables (Table 2 and Table 3).

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

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

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or study (see Section 8). In addition, all ventricular tachyarrhythmias are considered AEs of interest and should be reported to the Sponsor within 24 hours.

9.2.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the Schedule of Assessments Tables (Table 2 and Table 3).
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the Schedule of Assessments Tables (Table 2 and Table 3).
- The Sponsor will inform FDA within 7 days of any grade 2 or higher “alteration in personality-behavior or in mood” or “altered mental status” adverse events that occur in participants who have received GSK2838232.
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.5, Appendix 5. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the sponsor.
- NOTE: The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.5, Appendix 5.

9.2.2. Method of Detecting AEs and SAEs

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

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 3.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Section 12.5, Appendix 5.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met. In addition, all ventricular tachyarrhythmias are considered AEs of interest and should be reported to the Sponsor within 24 hours.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the

sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

- Please see the SRM for SAE reporting contact details.

9.2.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until the final follow-up visit.

- If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 12.6, Appendix 6.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.6. Total Blood Volume

No more than 500 mL of blood will be collected over the duration of the study, from an individual participant, including any extra assessments that may be required.

9.3. Treatment of Overdose

For this study, any dose of GSK2838232 greater than the planned dose for any given participant in each treatment period within a 24-hour time period (± 1 hour) will be considered an overdose.

For this study any dose of RTV greater than the planned dose (100 mg once daily) within a 24-hour time period (± 1 hour) will be considered an overdose.

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

- Contact the GSK Medical Monitor immediately.

- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until GSK2838232 can no longer be detected systemically (at least 7 days for GSK2838232).

- Obtain a plasma sample for PK analysis within 5 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 participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Table 2 and Table 3).

9.4.1. Physical Examinations

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

9.4.2. Vital Signs

- Vital signs will be measured in supine position after 10 minutes rest and will include systolic and diastolic blood pressure (BP) and heart rate (HR);
- BP and HR to be taken in triplicate (taken 5 minutes apart) at pre-dose (Part 1: Day 1; Part 2: Day 1 and Day 11) and singular at all other measurement time points;
- If a blood pressure is outside the normal limits (< 90 mmHg or > 160 mmHg), then additional measurements should be taken each minute for 2 more occasions.
- If a HR is outside the normal limits (< 40 bpm or > 100 bpm) then additional measurements should be taken 5 minutes apart for 2 more occasions.
- Ensure correct sized cuff is used for arm circumference.
- It is acceptable that HR be captured from continuous ECG equipment, 12-lead ECG or BP equipment.
- The GSK Medical Monitor should be notified for any clinically significant changes in vital signs.

9.4.3. Electrocardiograms

- Triplicate 12-lead ECGs will be obtained at least 5 minutes apart in the supine position after 10 minutes of rest pre-dose (Part 1: Day 1; Part 2: Day 1 and Day 11). All values will be recorded.
- Singular 12-lead ECGs will be recorded at all other timepoints using an ECG machine that automatically calculates the HR and measures PR, QRS, QT and QTcF intervals.

- Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- The Investigator will review the 12-lead ECGs. The decision to run repeat measurements if a result is outside of the normal predicted range (and/or considered clinically significant) should be made by the PI based on their clinical judgement to ensure participant safety.

9.4.4. Holter Monitoring

Cardiac monitoring (24 hour) will be performed using Holter monitoring during the screening process as shown in the Schedule of Assessments (Table 2 and Table 3). Holter monitoring may take place during the study period if needed.

Start date and time, stop date and time, interpretation, and nature of abnormality, if any, will be captured in the study database. Analysis of the Holter monitoring will consider the following:

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

9.4.5. Clinical Safety Laboratory Assessments

- Refer to Section 12.2, Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Assessments (Table 2 and Table 3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the Investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.

- All protocol-required laboratory assessments, as defined in Section 12.2, Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Table 2 and Table 3).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

9.5. Pharmacokinetics

9.5.1. Blood sample collection

- Blood samples for PK and metabolism analysis of GSK2838232 will be collected at the time points indicated in Schedule of Assessments (Table 2 and Table 3). 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. This will not require an amendment to the protocol.

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

9.5.2. Sample analysis

Concentrations of GSK2838232 will be determined in plasma using the currently approved bioanalytical methodology. Raw data will be archived in the GLP Archives, GSK.

- Once the plasma has been analyzed for GSK2838232, any remaining sample may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK, GlaxoSmithKline protocol.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

9.10. DATA MANAGEMENT

- For this study participant data will be entered into ClinBase, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by PAREXEL, and a copy of the annotated CRF will be sent to GSK. Participant initials will not be collected or transmitted to GSK according to GSK policy.

10. STATISTICAL CONSIDERATIONS

All statistical analyses will be performed by PAREXEL International Early Phase Biostatistics. All statistical analyses will be performed using the latest available version of SAS (SAS Institute Inc., Cary, North Carolina, United States of America [USA]), version 9.3 or higher. PK parameters will be calculated using Phoenix WinNonlin (Certara, L.P., 1699 S Hanley Road, St Louis MO 63144 USA), version 6.3 or higher.

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

Any deviations from the planned analyses will be described in the clinical study report.

10.1. Sample Size Determination

Sample sizes are based on prior relative bioavailability studies with GSK2838232 and take into account variability and logistical factors while no formal calculation of power or sample size for Parts 1 or 2 of the study was performed. A sample size of approximately 16 participants for Part 1 and 10 participants for Part 2, considering a drop-out rate of 25%, of the study should be sufficient to provide useful estimates of inter-participant variability for GSK2838232 PK parameters and safety assessments.

Additional participants will be randomized and enrolled to ensure a minimum of 12 evaluable participants for Part 1 (crossover of tablet and capsule) and 8 evaluable participants for Part 2 (6 active: 2 placebo).

Sample size assumptions

For Part 1 of the study: The between-subject variability (%CVb) for AUC(0-∞), and Cmax parameters from previous studies at different doses were 21% to 47% and 41% to 44%, respectively. Assuming within-subject variability (%CVw) for AUC(0-∞) and Cmax is 80% of highest between-subject variability (which will be 38% and 35%, respectively), and with the sample size of 12, it is estimated that the precision (i.e., half

width of the 90% confidence interval on the log scale) for the relative bioavailability assessment will be within 31.7% of the point estimate for AUC(0-∞), and within 29.0% of the point estimate for Cmax. If the point estimate of the ratio of geometric mean for Cmax is 1, then 90% confidence interval will be approximately (0.78, 1.29).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

All Participants Screened Population

The All Participants Screened Population will include all participants who consent to participate in the clinical study. Participants in this population will be used for disposition summary.

Safety Population

The Safety Population will include all participants who received at least 1 dose of the study treatment (including placebo) with at least 1 post-baseline safety assessment. Participants in this population will be used for all demographic and safety summaries or listings. The population will be defined separately for Part 1A, Part 1B and Part 2 of the study.

Pharmacokinetic Population

The PK Population will include all participants in the Safety population for whom at least one evaluable PK sample is obtained and analyzed. Pharmacokinetic samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded. All PK analyses will be based on this analysis population. The population will be defined separately for Part 1A, Part 1B, and Part 2 of the study.

10.3. Definition of Baseline

Unless specified, baseline will be the last value before the first dose of study treatment.

10.4. Statistical Analyses

All safety analyses will be performed on the Safety Population.

All PK analyses will be performed on the PK Population.

For assessment of relative bioavailability of tablet versus capsule (AUC(0-∞) and Cmax) and effect of food (AUC(0-∞), Cmax, and tmax), loge-transformed selected PK parameters (except tmax) will be analyzed using a mixed effects model. The point estimates and their associated 90% confidence interval (CI) will be provided for the

ratios, test/reference (for bioavailability) and fed/fasted (food effect) in PK parameter values on the original scale.

For the parameter tmax, the corresponding non-parametric analysis will be performed on the original scale using CIs for the estimation of the treatment difference.

Steady-state GSK2838232 concentrations will be assessed by estimating the slope of pre-dose concentrations following repeated daily administration. Accumulation of plasma GSK2838232 will be assessed as the ratios of Day 11/Day 1 AUC(0-τ), Cmax, and Cτ values.

10.4.1. Safety Analyses

Clinical safety observations will include AEs, vital sign measurements, ECGs and clinical laboratory measurements (hematology, clinical chemistry and urinalysis). Safety data will be tabulated and, where appropriate, analyzed by the use of descriptive statistics.

The number (%) of participants withdrawing from the study treatment, study and reason for withdrawal will be summarized for each treatment with placebo participants combined within each study part.

Reported AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of participants with treatment-emergent AEs (TEAEs) and treatment-related AEs will be tabulated by system organ class (SOC), preferred term and by treatment group within each study part. Severity of the TEAEs and treatment-related AEs will also be summarized by SOC, preferred term and by treatment group within each study part. Deaths, SAEs and AEs leading to withdrawal will be listed.

Descriptive statistics for observed and change from baseline in laboratory parameters (if applicable), vital signs measurements and ECGs will be presented by treatment group within each study part. Clinical laboratory toxicities will be graded based on the Division of AIDS (DAIDS) grading system, as specified in Section 12.4, Appendix 4. Summaries of laboratory toxicity grade will be provided.

10.4.2. Pharmacokinetic Analyses

The following plasma PK parameters will be determined using standard non-compartmental methods as data permit and in compliance with the GlaxoSmithKline SOP:

Part 1:

- AUC(0-t)
- AUC(0-∞)
- Cmax
- C24

- tlag
- tmax
- t½
- tlast

Part 2:

Day 1 dose:

- AUC(0-τ)
- Cmax
- Cτ
- tmax
- tlag

Day 11 dose:

- AUC(0-τ)
- AUC(0-∞)
- Cmax
- Cτ
- tmax
- t½
- tlast

Accumulation:

- R(AUC(0-τ))
- R(Cmax)
- R(Cτ)

Any additional PK parameters that are calculated will be provided in the RAP. Actual elapsed times from dosing will be used in the PK analysis. The AUC will be determined using the linear-up/log-down trapezoidal rule. Individual PK parameter values will be listed, and a descriptive summary by treatment will be provided.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. Plasma GSK2838232 concentration-time data will be listed by participant, treatment group and time and summarized by treatment group and time for each part of the study. Individual participant profiles for GSK2838232 concentration-time data will be presented on both a linear and semi-log scale. Linear and semi-log figures for mean and median GSK2838232 plasma concentrations versus time will also be generated.

10.4.2.1. Relative Bioavailability

In Part 1A, the following plasma PK parameters will be assessed to determine the relative bioavailability as data permit:

- AUC(0-∞)
- Cmax

The dependent variable will be the log-transformed PK parameters of interest (AUC(0-∞) and Cmax) and the independent variables will include a fixed effect for treatment (table or capsule), sequence and period, and participant as a random effect. The estimated difference and CI obtained on the log scale will be exponentiated to provide an estimate of the table to capsule ratio and its associated 90% CI.

10.4.2.2. Food Effect

Food effect will be assessed in Part 1 using Analysis of Variance (ANOVA). The dependent variable will be the log-transformed PK parameters of interest (AUC(0-∞) and Cmax) and the independent variables will include a fixed effect for treatment (with or without food) and subject as a random effect. The estimated difference and confidence interval (CI) obtained on the log scale will be exponentiated to provide an estimate of the fed to fasted ratio and its associated 90% CI.

10.4.2.3. Steady State Assessments

For Part 2, mean plasma GSK2838232 pre-dose values between Days 2 through 11 and $C\tau$ of Day 11 will be plotted against time. Achievement of plasma GSK2838232 steady-state will be assessed by calculating the 90% CI of the slope of the linear regression of log ($C\tau$) versus time. The dependent variable in the linear regression model will be log ($C\tau$) and the model will include a random intercept effect for participant and a fixed slope effect for study day. Steady state will be reached if the 90% CI for the slope estimate includes zero.

10.4.2.4. Accumulation

For Part 2, the extent of accumulation of GSK2838232 will be evaluated by comparing AUC(0-τ), Cmax and $C\tau$ between Day 11 and Day 1. For each of these comparisons an analysis of variance will be conducted on the log scale. The difference between Day 11 and Day 1 least square (LS) means and a 90% CI will be computed by fitting a mixed effects model with the log-transformed PK parameter as the dependent variable, day as a fixed effect and participant as a random effect. The estimated difference and confidence interval obtained on the log-scale will be exponentiated to provide an estimate of the Day 11 to Day 1 ratio and its associated 90% CI. If the model fails to converge, participants will be fit as a fixed effect.

10.4.3. Efficacy Analyses

Not applicable.

10.4.4. Other Analyses

Not applicable.

10.4.5. Interim Analyses

The dose and formulation to be administered in Part 1B and Part 2 will be decided, based on the outcome and results of an informal analysis of data from Part 1A of the study.

The Reporting and Analysis Plan will describe the planned interim analyses in greater detail.

11. REFERENCES

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U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Dietary Guidelines for Americans, 2010*. 7th Edition, Washington, DC: U.S. Government Printing Office, December 2010.

United Nations program on HIV/AIDS (UNAIDS), Fact Sheet 2015. Available from www.UNAIDS.org

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC (0-t)	Area under the concentration-time curve from zero up to a definite time t
AUC(0-τ)	Area under the curve (Area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state)
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AV	Atrioventricular
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
Cmax	Maximum observed concentration
Con Med	Concomitant medication
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CV	Cardiovascular
CYP	Cytochrome P subfamily of enzymes
DAIDS	Division of AIDS
DDI	Drug-drug Interaction
ECG	Electrocardiogram
ERCP	Endoscopic retrograde cholangio-pancreatography
FDA	Food and Drug Administration
FSH	Follicle Stimulating
FTiH	First Time in Human
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HbsAg	Hepatitis B surface Antigen
hCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
Hem/Chem	Hematology and Clinical Chemistry
HIV	Human Immunodeficiency Virus

HR	Heart Rate
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
IEC	Independent Ethics Committees
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NOAEL	No Adverse Event Dose Level
PI	Principal Investigator
PiB	Powder in Bottle
PK	Pharmacokinetic(s)
QD	Once daily
RAP	Reporting and Analysis Plan
RTV	Ritonavir
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SSD	Spray Dried Dispersion
SUSAR	Suspected Unexpected Serious Adverse Reactions
t1/2	Apparent terminal phase half-life
TEAE	Treatment-Emergent Adverse Event
tlag	Lag-time (time delay between drug administration and first observed
tmax	Time of occurrence of Cmax
ULN	Upper Limit of Norma
US	United States (of America)
WOCBP	Women of child bearing potential
WPW	Wolf Parkinson White syndrome

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Norvir
Phoenix
SAS
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Hematology</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</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>Aspartate Aminotransferase (AST) / Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine Aminotransferase (ALT) / Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Albumin</td></tr>
<tr><td>Triglycerides</td><td colspan="3">Cholesterol (total cholesterol, HDL, LDL, VLDLc (calculated) and Non-HDLc [calculated])</td></tr>
<tr><td>Lipase</td><td colspan="3"></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)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
FSH and estradiol (as appropriate)
Serum hCG Pregnancy test (as appropriate)[2]</td></tr>
<tr><td colspan="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 8.1.1 and Section 12.2, Appendix 2.
[2]Serum testing will be performed at Screening testing.</td></tr>
</table>

12.3. Appendix 3: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

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

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><td colspan="2">Liver Chemistry Stopping Criteria</td></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 3 x ULN

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

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><td colspan="2">Required Actions and Follow up Assessments</td></tr>
<tr><td>Actions</td><td>Follow Up Assessments</td></tr>
<tr><td>• Report the event to GSK within 24 hours

• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]

• Perform liver event follow up assessments

• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT ≥ 3 x ULN AND bilirubin ≥ 2 x ULN or INR > 1.5

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up</td><td>• Viral hepatitis serology[3]

• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend

• Obtain blood sample for pharmacokinetic (PK) analysis.

• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

• Fractionate bilirubin, if total bilirubin ≥ 2 x ULN

• 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</td></tr>
</table>

Liver Chemistry Stopping Criteria	
assessments within **24 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **If ALT ≥ 3 x ULN AND bilirubin < 2 x ULN and INR ≤ 1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **If ALT ≥ 3 x ULN AND bilirubin ≥ 2 x ULN or INR > 1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN. 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 ≥ 3 x ULN and bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or ALT ≥ 3 x ULN and INR > 1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants.

3. 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.

12.4. Appendix 4: Division of AIDS Table For Grading The Severity of Adult and Pediatric Adverse Events

The DAIDS Table [Division if AIDS (DAIDS) Table (NIH), 2014] will be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

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

Major Clinical Conditions Grading Table

Cardiovascular:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities 1 ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg	≥ 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
<18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile +5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 9th 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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac Ischemia or Infarction *Report only one*	Not applicable	Not applicable	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Haemorrhage (with significant acute blood loss)	Not applicable	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 ≥ 06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Thrombosis or Embolism *Report only one*	Not applicable	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

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

Dermatologic:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Not applicable	Not applicable
Bruising	Localized to one area	Localized to more than one area	Generalized	Not applicable
Cellulitis	Not applicable	Non-parenteral treatment indicated (e.g., oral antibiotics,	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	Not applicable	Not applicable
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	Not applicable	Not applicable
Petechiae	Localized to one area	Localized to more than one area	Generalized	Not applicable

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritus[1] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional	Itching causing inability to perform usual social & functional activities	Not applicable
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

1. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section

Endocrine and Metabolic:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non- ketotic coma, end organ failure)
Gynaecomastia	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	Not applicable
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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 1	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	Not applicable
Lipohypertrophy 2	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	Not applicable

1. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
2. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional	Symptoms causing inability to perform usual social & functional activities	Not applicable
Cholecystitis	Not applicable	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	Not applicable	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diarrhoea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	Not applicable	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, haemorrhage, sepsis)
Perforation (colon or rectum)	Not applicable	Not applicable	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	Not applicable	Not applicable
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional	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	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	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	Not applicable	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 1 ≥ *30 years of age*	BMD t-score -2.5 to -1	Not applicable	Not applicable	Not applicable
<*30 years of age*	BMD z-score -2 to -1	Not applicable	Not applicable	Not applicable

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteoporosis 1 ≥ *30 years of age*	Not applicable	BMD t-score <-2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral	Pathologic fracture causing life-threatening consequences
<30 years of age	Not applicable	BMD z-score <-2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

1. **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 Center for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	Not applicable	Not applicable	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, Behavioural, 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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	Not applicable	Not applicable	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	Not applicable	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	Not applicable

Pregnancy, Puerperium and Perinatal:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Foetal Death or Stillbirth (report using mother's participant ID)	Not applicable	Not applicable	Foetal loss occurring at ≥ 20 weeks gestation	Not applicable
Preterm Delivery 1 (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 Miscarriag[2] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	Not applicable

1. Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
2. Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.

Psychiatric:

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

Respiratory:

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

Sensory:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	Not applicable	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., > 50 dB audiogram and < 50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech- language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	Not applicable

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal oedema
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	Not applicable
Cytokine Release Syndrome 1	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥3 8.6 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 2 (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 3	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 4 > 5 to 19 years of age	Not applicable	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	Not applicable	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	Not applicable	WHO Weight-for-length z-score < -2 to ≤ -3	WHO Weight-for- length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Weight Loss (excludes postpartum weight loss)	Not applicable	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)

1. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
2. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
3. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnoea
4. WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age

Urinary:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	Not applicable	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness 1 *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 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)

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of*	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	Not applicable

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

Laboratory Values – Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	Not applicable	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	Not applicable
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	Not applicable	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*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Bilirubin *Direct Bilirubin 1, High* *>28 days of age*	Not applicable	Not applicable	>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	See Section 12.4.1. Total Bilirubin for Term and Preterm Neonates	See Section 12.4.1. Total Bilirubin for Term and Preterm Neonates	See Section 12.4.1. Total Bilirubin for Term and Preterm Neonates	See Section 12.4.1. 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 *≥ 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	Not applicable	Not applicable	Not applicable	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

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Creatinine Clearance 2 or eGFR, Low *Report only one*	Not applicable	< 90 to 60 mL/min or mL/min/1.73 m^2 OR 10 to < 30% decrease from baseline	< 60 to 30 mL/min or mL/min/1.73 m^2 OR ≥30 to <50% decrease from baseline	< 30 ml/min or mL/min/1.73 m^2 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*
<1 month of age	50 to 54 *2.78 to 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH< 7.3 without life-threatening consequences	Increased lactate with pH< 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

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*	Not applicable
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	Not applicable
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*	Not applicable
> 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*	Not applicable
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 3, 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*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
<1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 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*

1. 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
2. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2)
3. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114

Hematology:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm3; *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/mm3; *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 <0.500x10^9*	< 350 *< 0.350x10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm3; *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 109 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 109 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
Haemoglobin 1**, Low** (g/dL; *mmol/L*) 2				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to <13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Methaemoglobin (% haemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3*; cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 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*

1. Male and female sex is defined as sex at birth.
2. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading haemoglobin 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.

Urinalysis:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	Not applicable
Haematuria (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	Not applicable

12.4.1. Total Bilirubin Table for Term and Preterm Neonates:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin 1**, High** (mg/dL; *µmol/L*) 2 ***Term Neonate*** 3 *<24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to <171*	10 to < 17 *171* to *<290.7*	≥ 17 ≥ *290.7*
24 to <48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 ≥ *324.9*
48 to <72 hours of age	8.5 to < 13 *145.35 to <222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 ≥ *376.2*
72 hours to <7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 ≥ *410.4*
7 to 28 days of age *(breast feeding)*	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age *(not breast feeding)*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate20 *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	Not applicable	Not applicable	10 to < 14 *171 to < 239.4*	≥ 14 ≥ *239.4*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
28 to < 32 weeks gestational age and < 7 days of age	Not applicable	Not applicable	6 to < 10 *102.6 to < 171*	≥ 10 ≥ *171*
< 28 weeks gestational age and < 7 days of age	Not applicable	Not applicable	5 to < 8 *85.5 to < 136.8*	≥ 8 ≥ *136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

1. Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.
2. A laboratory value of 1 mg/dL is equivalent to 17.1 μmol/L.
3. Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35weeks gestational age; and neonate, as 0 to 28 days of age.

12.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

12.5.1. Definition of Adverse Events

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

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

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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).

A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

c. Results in death

d. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

e. Requires inpatient hospitalization or prolongation of existing hospitalization

NOTE:

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

f. Results in persistent 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 with 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 SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Section 12.2, Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Recording Adverse Events and Serious Adverse Events

Adverse Events and Serious Adverse Events Recording

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

12.5.4. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity

- The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

Follow-up of AE and SAE
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

12.5.5. Reporting of Serious Adverse Events to GSK

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

12.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

7. Premenarchal
8. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

9. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 6.1):
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus an additional method of contraception with a failure rate of < 1% per year when having penile-vaginal intercourse with a woman of childbearing potential as described in Table 6.

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration (during the protocol-defined time frame).
- Refrain from donating sperm for duration of study and for 3 months after study completion or from last dose.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 6.

Table 6 Highly Effective Contraceptive Methods

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

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test
- Additional pregnancy testing may be performed at the discretion of the Investigator during the treatment period or after the last dose of study treatment and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing will be performed using the test kit provided by the central laboratory.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours 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.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on participant and neonate, 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. 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 participant who becomes pregnant while participating will be withdrawn from the study.

12.7. Appendix 7: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
    - Applicable ICH Good Clinical Practice (GCP) Guidelines.
    - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained . The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

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

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g.,

laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

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

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

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

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