Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for A Phase 2a, Multicenter, Randomized, Adaptive, Open-label, Dose Ranging Study to Evaluate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Cobicistat-boosted GSK2838232 Monotherapy Over 10 Days in HIV-1 Infected Adults
Compound Number	:	GSK2838232
Effective Date	:	11-May-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Study 200911.
- This RAP is intended to describe the safety, tolerability, pharmacokinetic, and antiviral analyses required for the study.
- This RAP will be provided to the study team members and CRO (PPD) to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Senior Reviewer, PPD	11-May-2018
PPD Lead Statistician, PPD	11-May-2018

RAP Team Approvals:

Approver	Date	Approval Method
PPD Director (Clinical Pharmacology), GSK	30-APR-2018	Email Approval
PPD Director (Clinical Development), GSK	01-MAY-2018	eSignature
PPD Executive Medical Director (SM), GSK	30-APR-2018	Email Approval
PPD Director (Clinical Pharmacology Modelling and Simulation), GSK	30-APR-2018	Email Approval
PPD Medical Director (SERM), GSK	30-APR-2018	Email Approval
PPD Manager (Clinical Data Management), GSK	03-MAY-2018	Email Approval
PPD Manager (Clinical Development), GSK	02-MAY-2018	Email Approval

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Data Analyst Statistician (Clinical Statistics)	30-APR-2018	Signature
PPD Statistics Leader (Clinical Programming)	30-APR-2018	Signature
PPD Senior Statistics Director (Clinical Statistics), GSK	30-APR-2018	Signature
PPD Programming Manager, GSK	01-MAY-2018	Signature
PPD Programming Manager, GSK	03-MAY-2018	Signature

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Study 200911.
Protocol	• This RAP is based on the protocol amendment 3 (Dated: 15Jun2017) of Study 200911 (GSK Document No.: 2015N227852_03) and eCRF Version 1.0.
Primary Objectives	• To evaluate antiviral activity of GSK2838232/Tybost (cobicistat,cobi) in HIV-1 infected patients during 10 days of monotherapy. • To assess safety and tolerability of GSK2838232/cobi when administered as monotherapy over 10 days. • To characterize the pharmacokinetics of GSK2838232 in HIV-1 infected patients following GSK2838232/cobi dosing for 10 days.
Primary Endpoints	• Maximum decline from baseline and change from baseline (Day 1) in plasma HIV-1 RNA. • Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, electrocardiogram (ECG) and vital signs assessments. • GSK2838232 PK parameters following dose administration, as follows: Day 1: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); Following last repeat administration on Day 10: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Study Design	• This is a Phase 2a, multicenter, open-label, adaptive, dose ranging study.
Planned Analyses	• The final analysis will be performed after the completion of the study and final datasets authorization.
Analysis Populations	• Intent to Treat Exposed Population (ITT): defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received at least 1 dose of treatment and at least one post-baseline HIV-1 RNA measurement. This will be the primary population for the final efficacy analysis for all active treatment groups. • Per Protocol Population (PP): defined as all subjects who meet study criteria and are enrolled into the study with documented evidence of having received all doses and all post-baseline HIV-1 RNA measurement, with exceptions of major protocol deviation.

Overview	Key Elements of the RAP
	• Safety Population: defined as all subjects who are enrolled into the study with documented evidence of having received at least 1 dose of study treatment. • Pharmacokinetic Population: includes all subjects who receive GSK2838232 and undergo plasma PK sampling during the study. Subjects for whom a plasma PK sample is obtained and assayed will be included in the listing of plasma GSK2838232 concentration-time data. Results from samples collected from a subject with emesis occurring within 4 hours of the dose will not be considered as evaluable. • Pharmacokinetic/ Pharmacodynamic Population: Subjects who meet criteria for Per-Protocol and Pharmacokinetic Population analysis sets and who undergo PD sampling during the study.
Hypothesis	• No formal hypothesis will be tested.
Primary Analyses	• Both the PP and ITT Populations will be used for all efficacy analyses if there are exclusions from the Per Protocol population. Plasma HIV-1 RNA maximum decline and change from baseline during the study will be calculated for each subject on each assessment day. Plasma HIV-1 RNA will be listed by treatment, subject, and assessment day and summarized by treatment and assessment day along with change from baseline. Plots of mean and median plasma HIV-1 RNA actual and change from baseline data will be generated by treatment and assessment day. Plasma HIV-1 RNA maximum decline from baseline will be calculated for each subject and summarized by treatment. Together, the data from Parts A and B will be used to investigate the complete dose-response curve and the impact of lower doses on potential development of resistance. A dose-response curve will be fit to the data from Parts A & B. • Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library standards and data will be in CDISC format. No formal statistical analysis of the safety data will be conducted. • Plasma GSK2838232 concentration-time data will be analysed by non-compartmental methods with WinNonlin Version 6.4 or higher. Calculations will be based on the actual sampling times recorded during the study. Results based on samples collected from a subject with emesis within 4 hours of the dose will not be considered as evaluable. All PK data will be stored in the R&D archives, GlaxoSmithKline. Pharmacokinetic data will be presented in graphical and tabular form and will be summarized descriptively. Plasma GSK2838232 PK parameters, with the exception of tmax and tlag, will be log-transformed prior to analysis. Dose proportionality of plasma GSK2838232 PK parameters from Day 1 [AUC(0-24) and Cmax] and Day 10 [AUC(0-τ) and Cmax] will be assessed

Overview	Key Elements of the RAP
	using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI. The accumulation ratio (R) and steady-state assessments will be performed, if quality of the data permits. Comparisons of Day 10 with Day 1 PK for each dose will be used for the accumulation ratio (R) evaluation. Pre-dose concentrations between Days 7-10 will be used for steady-state assessment.
Secondary Analyses	• Relationships between various pharmacokinetic parameters (e.g., AUC, Cmax, $C\tau$, etc.) and pharmacodynamic measures (e.g., log10 reduction from baseline in plasma HIV-1 RNA on Day 11) or safety parameters will be explored using various models including Emax and linear models. The relationship between dose and pharmacodynamic measures will also be explored. • Viral genotypic/phenotypic data will be listed and descriptive summaries will be provided. Details of the analyses will be provided in the clinical virology report.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

In protocol amendment 3 (Dated: 15/JUN/2017), the Safety Population is defined as all subjects who are enrolled into the study with documented evidence of having received at least 1 dose of assigned treatment. The Safety Population is defined in the RAP as all subjects who are enrolled into the study with documented evidence of having received at least 1 dose of study treatment.

2.2. Study Design

Overview of Study Design and Key Features

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

1. Part A Cohort 1 safety/PK/virology data was evaluated at interim, prior to initiating other cohorts in Part B, which are planned to run in a sequential fashion. All doses will be given with 150 mg cobicistat.
2. More doses/cohorts (including potential removal of cobi co-dosing) may be added (the maximum dose in Part B would not exceed 200 mg with cobicistat unless overall plasma exposure [as AUC and Cmax] was lower in HIV infected subjects than in healthy subjects at the same dose level).
3. Two subjects who were enrolled in Cohort 1 were mis-dosed at 50 mg GSK2838232 for 10 days. These 2 subjects will be included in and analysed with Cohort 3.

Design Features	• This is a Phase 2a, multicenter, open label, adaptive dose ranging, study to evaluate the antiviral effect, safety, tolerability, and PK of GSK2838232/cobi monotherapy over 10 days in HIV-1 infected adults who are not currently receiving ART therapy. To minimize the number of subjects exposed to suboptimal doses, an adaptive and dose ranging design is applied in this study. • This study consists of a screening visit, a 10-day treatment period, and follow-up evaluations for 2 weeks following last dose. • Screening will be performed as the patients are identified, within 30 days of the first dose of study drug. Eligible HIV-1 infected subjects will receive study treatments for 10 days.
Dosing	• All subjects enrolled in Part A will receive 100 mg GSK2838232 and 150 mg cobicistat daily for 10 days. • Following the interim analysis of safety, virology and PK data from the first cohort of subjects in Part A, the dose levels for Part B were determined to be 200 mg, 50 mg, and 20 mg GSK2838232 and 150 mg cobicistat.
Treatment Assignment	• Subjects will be assigned to treatment (active), prior to the start of the study, using validated internal software.
Interim Analysis	• An interim analysis of preliminary safety, tolerability, PK and antiviral activity occurred after subjects of Part A Cohort 1 completed their Day 13 visit and is described in a separate reporting and analysis plan.

2.3. Statistical Hypotheses

The primary objectives of this study are to investigate the safety, tolerability, and antiviral activity of GSK2838232 administered as monotherapy in combination with cobicistat in HIV-1 infected subjects, over a 10-day treatment period. The antiviral activity will be assessed by estimating plasma HIV-1 RNA max change from baseline during the study. No formal hypotheses will be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

An interim analysis of preliminary safety, tolerability, PK and antiviral activity occurred after subjects of Part A Cohort 1 completed their Day 13 visit. Full details of the interim analysis are described in a separate reporting and analysis plan. Based on the results of the interim analysis, the dose levels for Part B were determined to be 200 mg, 50 mg, and 20 mg GSK2838232 with 150 mg cobicistat.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

Data will be listed and summarized according to GlaxoSmithKline reporting standards, where applicable. Listings will be sorted by subject, day and time, noting treatment; summaries will be presented by treatment, day, and time. Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), median, minimum, and maximum, whereas n and percent will be used as summary statistics for categorical variables. Baseline or predose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables. Version 9.3 or higher of the SAS system will be used to analyse the data as well as to generate tables, figures, and listings.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Screened	• Comprise all subjects who consented to participate in the clinical trial and were screened.	• Summarize the screen failure subjects
Safety	• Comprise of all subjects who receive at least one dose of study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Safety

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat Exposed	• Comprise of all subjects who meet study criteria and are enrolled into the study with documented evidence of having received at least 1 dose of treatment and at least one post-baseline HIV-1 RNA measurement. • This population will be based on the treatment which the subject actually received.	• Efficacy
Per-Protocol	• Comprise of all subjects who meet study criteria and are enrolled into the study with documented evidence of having received all doses and all post-baseline HIV-1 RNA measurement, with exceptions of those who have at least one major protocol deviation. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population).	• Efficacy
Pharmacokinetic	• Subjects who receive GSK2838232 and undergo plasma PK sampling during the study. Subjects for whom a plasma PK sample is obtained and assayed will be included in the listing of plasma GSK2838232 concentration-time data. Results from samples collected from a subject with emesis occurring within 4 hours of the dose will not be considered as evaluable.	• Pharmacokinetic
Pharmacokinetic/ Pharmacodynamic	• Subjects who meet criteria for Per-Protocol and Pharmacokinetic Population analysis sets and who undergo PD sampling during the study.	• Pharmacokinetic/ Pharmacodynamic

NOTES:

- Please refer to Appendix 12: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
12.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
12.2	Appendix 2: Time & Events
12.3	Appendix 3: Assessment Windows
12.4	Appendix 4: Treatment States and Phases
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
12.8	Appendix 8: Values of Potential Clinical Importance
12.9	Appendix 9: Population Pharmacokinetic Analyses
12.10	Appendix 10: Pharmacodynamic / Biomarker Analysis
12.11	Appendix 11: Abbreviations & Trade Marks
12.12	Appendix 12: List of Data Displays
12.13	Appendix 13: Model Checking and Diagnostics for Statistical Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the Safety population, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 12 List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition	Y		
Reasons for Screening Failure	Y		Y
Study Treatment Discontinuation	Y		Y
Reasons for Study Withdrawal			Y
Planned and Actual Treatment Assignment			Y
Subjects at Each Visit	Y		
Protocol Deviations			
Summary of Protocol Deviations	Y		Y
Deviations Leading to Exclusions from Per Protocol Population	Y		[1]
Inclusion/Exclusion Criteria Deviations	Y		Y
Populations analysed			
Study Populations	Y		Y
Number of Subjects by Centre	Y		
Subjects Excluded from Any Population			Y
Demography & Disease Characteristics at Screening			
Demographic Characteristics	Y		Y
Race & Racial Combinations	Y		Y
Race & Racial Combination Details	Y		
Cardiovascular Risk Assessment			Y
Family History of Cardiovascular Risk	Y		
HIV Risk Factors			Y
Substance Use	Y		
Medical Condition & Prior and Concomitant Medications			
Cardiovascular Medical Conditions	Y		Y
Medical Conditions (Current/Past)	Y		Y
Medication (Concomitant/Prior)	Y		Y

	Data Displays Generated		
	Table	Figure	Listing
Relationship Between ATC Level 1, Ingredients and Verbatim Text			Y
HIV Associated Conditions			Y
Exposure and Treatment Compliance			
Study Treatment Overall Compliance	Y		
Exposure to Study Treatment	Y		Y

[1] Subjects with protocol deviations leading to exclusions from Per Protocol population will be listed in Listing of Subjects Excluded from Any Population

6.2. Display Details

6.2.1. Subject Disposition

The disposition table will consist of all intent-to-treat subjects

The number and percentage of subjects who failed screening and were, therefore, not entered into the study, overall and by reason, will be summarized. A listing of the screen failure record for all subjects who failed screening, including the reasons for screen failure will be produced.

Reasons for study treatment discontinuation will be summarized for each treatment group and overall. A by-subject listing of reasons for study withdrawal, a by-subject listing of reasons for study treatment discontinuation, and a by-subject listing of planned and actual treatment received will be produced.

The number and percentage of subjects at each visit will be summarized for each treatment group and overall.

6.2.2. Protocol Deviations

The number and percentage of subjects who had important protocol deviations defined in Section 12.1 will be summarized overall and by treatment group.

A listing of important protocol deviations will be produced.

Protocol deviations leading to exclusion from Per Protocol population will be summarized (see Section 12.1 for protocol deviations, which may lead to the exclusion of a subject from the Per Protocol population).

Subjects excluded from the Per Protocol population can be found in the listing of subjects excluded from any populations (see below).

Inclusion and exclusion criteria deviations will be summarized and listed.

6.2.3. Populations analysed

The number of subjects who were enrolled into the study, and the number of subjects within each analysis population (ITT, Per Protocol, Safety and PK) will be summarized for each treatment group and overall. A by-subject listing showing inclusion within each study population will be produced.

The number and percentage of subjects will be summarized by centre for each treatment group and overall.

Subjects excluded from any population, including subjects excluded from the Per Protocol population, will be listed.

6.2.4. Demography

The demographic and baseline characteristics age, sex, race, ethnicity, height, weight, BMI, and baseline CDC HIV-1 classification will be summarized by treatment group and overall for the ITT population. The count, mean, standard deviation, median, minimum, and maximum value will be computed for age, BMI, height, and weight.

A by-subject listing of demographic and baseline characteristics will also be produced.

Summaries of race and racial combinations will be produced for each treatment group and overall. A listing of race by subject will also be produced.

Summaries of family history of cardiovascular risk and substance use history will be provided by treatment group and overall. Cardiovascular risk assessment by subject will be listed.

A listing of HIV risk factors and mode of transmission by subject will be produced.

6.2.5. Medical Conditions and Medications

6.2.5.1. Medical Conditions

The number and percentage of subjects with each past and current medical condition will be reported for each treatment group and overall. Past conditions are those reported as ‘past’ and current conditions are those reported as ‘current’ at screening. Past and current conditions will be reported separately. Medical conditions will be coded using the Medical Dictionary for Regulatory Activities (current MedDRA version at the time of DBR) and reported by system organ class (SOC) and preferred term (PT). By-subject listings of past and current medical conditions will also be produced.

A summary of cardiovascular medical conditions will be provided by treatment group and overall, and a by-subject listing will be produced.

A by-subject listing for HIV associated conditions will be produced.

6.2.5.2. Medications

For reporting purposes, medications will be classified as prior, concomitant, and/or post-treatment using the associated start and stop dates recorded in the eCRF and relative to the first and last dose dates of investigational product (IP) (see Appendix 4). Medications will be coded using the GSK Drug coding dictionary (current version at the time of DBR).

Concomitant and prior medications will be summarised by GSK-Drug Anatomical Therapeutic Chemical (ATC) classification level 1 (body system) and ingredient. Drugs that are composed of a combination of ingredients will be displayed according to the ATC classifications of the ingredients, not of the combination.

The relationship between ATC level 1, ingredients and verbatim text for all medications in the study will be listed.

6.2.6. Exposure and Treatment Compliance

The complete dosing experience will be listed for all subjects. The total duration of exposure (number of days on study drug), average daily dose, and cumulative dose will be summarized by treatment group.

For subjects who completed the 10-day treatment period in Part A and in Part B of the study, the expected number of doses during each treatment period is 10. For subjects who permanently discontinued the study treatment and/or withdrew from the study, the expected number of doses during the treatment period will be calculated using "Days on study drug" where "Days on study drug" is Last Dose Date – First Dose Date +1.

A summary of study medication compliance will be produced by treatment group: 0%, >0-<100%, 100%, >100%. The compliance will be calculated for the whole study treatment period as the percentage of cumulative dose [100*(actual cumulative dose) / (expected cumulative dose for the subject's treatment duration)].

For subjects who completed the 10-day treatment period in either Part A or Part B, the expected cumulative dose of GSK2838232 taken during the treatment period is as follows:

Part A

- For subjects who received 100 mg GSK2838232, the expected cumulative dose is 1,000 mg GSK2838232 (the 100 mg of IP is comprised of two 50 mg capsules of GSK2838232 administered daily over the 10-day treatment period)

Part B

- For subjects who received 200 mg GSK2838232, the expected cumulative dose is 2,000 mg GSK2838232 (the 200 mg of IP is comprised of four 50mg capsules of GSK2838232 administered daily over the 10-day treatment period)

- For subjects who received 50 mg GSK2838232, the expected cumulative dose is 500 mg GSK2838232 (the 50 mg of IP is comprised of one 50 mg capsules of GSK2838232 administered daily over the 10-day treatment period)
- For subjects who received 20 mg GSK2838232, the expected cumulative dose is 200 mg GSK2838232 (the 20 mg of IP is comprised of one 20 mg capsule administered daily over the 10-day treatment period).

Each daily dose of GSK2838232 is taken with 150 mg cobicistat. The expected cumulative dose of cobicistat taken during the 10-day treatment period is 1,500 mg.

For subjects who permanently discontinued study treatment or withdrew early from the study, the expected cumulative dose of GSK2838232 taken during the treatment period will be calculated as follows:

Part A

- For subjects who received 100 mg GSK2838232, the expected cumulative dose is 100 mg*(Last Dose Date – First Dose Date +1)

Part B

- For subjects who received 200 mg GSK2838232, the expected cumulative dose is 200 mg*(Last Dose Date – First Dose Date +1)
- For subjects who received 50 mg GSK2838232, the expected cumulative dose is 50 mg*(Last Dose Date – First Dose Date +1)
- For subjects who received 20 mg GSK2838232, the expected cumulative dose is 20 mg*(Last Dose Date – First Dose Date +1)

For subjects who permanently discontinued study treatment or withdrew early from the study, the expected cumulative dose of cobicistat taken during the treatment period is 150 mg*(Last Dose Date – First Dose Date + 1).

The actual cumulative dose of GSK2838232 for all subjects is the sum of all doses, in mg, of study drug consumed for the duration of the study. Similarly, the actual cumulative dose of cobicistat for all subjects is the sum of all doses, in mg, of study drug consumed for the duration of the study.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

Both the Per Protocol and Intent-To-Treat populations will be used for all efficacy analyses if there are subjects excluded from the Per Protocol population. If there are no exclusions (i.e., if the Per Protocol and Intent-To-Treat population do not differ), then the Intent-To-Treat population will be used for all efficacy analyses.

Table 3 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 12 List of Data Displays.

Table 3 Overview of Planned Efficacy Analyses

	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Viral Load														
Plasma HIV-1 RNA				Y			Y							
Change from baseline (Day 1) to Day 11 and maximum decline from baseline in plasma HIV-1 RNA											Y	Y		
Proportion of subjects with plasma HIV-1 RNA <400 and < 50 copies/mL				Y										
Proportion of subjects with plasma HIV-1 RNA change from baseline >1.5 log10 copies/mL decrease											Y			
Summary of modelled Plasma HIV-1 RNA mean rate of decline and maximum decline											Y			

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.1.1.1. Viral Load

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

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

Plasma HIV-1 RNA maximum decline from baseline and time to nadir will be calculated for each subject and summarized by treatment.

Plasma HIV-1 RNA values will be averaged on the days that it is collected twice (Days 1, 10, and 11) for baseline and corresponding post-baseline assessments.

Plasma HIV-1 RNA values below LLOD or above ULOD will be imputed as: <400 copied/mL to 399, <50 copies/mL to 49, and >75000 copies/mL as 75001.

7.1.2. Planned Efficacy Statistical Analyses

Plasma HIV-1 RNA change from baseline to Day 11, and also maximum decline from baseline will be fitted in a mixed-effects linear model by treatment, with baseline plasma HIV-1 RNA and day fitted as fixed effects and subject fitted as a random effect. Estimated mean rate of decline (i.e., slope of day) with corresponding 90% CI will be provided for each treatment.

Proportion of subjects with plasma HIV-1 RNA <400 and < 50 copies/mL and proportion of subjects with plasma HIV-1 RNA change from baseline >1.5 $\log_{10}$ copies/mL decrease will be summarized by treatment and visit for ITT and PP Population.

Primary Statistical Analyses
Endpoints
• Change from baseline to Day 11 in Plasma HIV-1 RNA • Maximum decline from baseline in Plasma HIV-1 RNA
Model Specification
• Plasma HIV-1 RNA change from baseline to Day 11, and also maximum decline from baseline will be fitted in a mixed-effects linear model by treatment, with baseline plasma HIV-1 RNA and day fitted as fixed effects and subject fitted as a random effect.
Model Results Presentation

• Statistical analysis for change from baseline and maximum decline from baseline will be presented in tabular format. The linear model will be used to provide slope, intercept and a 90% CI of the slope.
 	
Example SAS Code:
 	
proc mixed data=dataset
class dose day subjid;
model plasma = baseplas day dose;
random subjid / type=un solution;
run;

7.2. Safety Analyses

7.2.1. Overview of Planned Safety Analyses

The primary safety analyses will be based on the Safety population, unless otherwise specified.

Table 4 provides an overview of the planned safety analyses, with full details of data displays being presented in Appendix 12 List of Data Displays.

Table 4 Overview of Planned Safety Analyses

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events								
Adverse Events Overview	Y							
All Adverse Events	Y			Y				
Subject Numbers for Individual AEs				Y				
Summary of All Adverse Events by Maximum Grade and SOC and PT	Y							
Summary of Drug-Related Adverse Events by Maximum Grade and SOC and PT	Y							
Drug Related Adverse Events	Y			Y				
Serious Adverse Events	Y			Y				
Drug Related Serious Adverse Events				Y				
Adverse Events Leading to Withdrawal from Study/Permanent Discontinuation of Study Treatment	Y			Y				
Common Adverse Events and Common Non-Serious Adverse Events By Overall Frequency	Y							
Fatal AEs				Y				
Non-Fatal SAEs				Y				
AEs of Special Interest	Y			Y				

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Laboratory Values								
Clinical Chemistry by Visit	Y			Y	Y			
Haematology by Visit	Y			Y	Y			
Liver Function by Visit	Y			Y	Y			
Treatment Emergent Clinical Chemistry Toxicities	Y							
On-Treatment Lab Abnormalities Worsened from Baseline by Maximum Grade - Chemistry	Y							
Treatment Emergent Haematology Toxicities	Y							
On-Treatment Lab Abnormalities Worsened from Baseline by Maximum Grade - Haematology	Y							
Treatment Emergent Liver Toxicities	Y							
On-Treatment Lab Abnormalities Worsened from Baseline by Maximum Grade – Liver Events	Y							
Liver Function Lab Abnormalities of Potential Clinical Importance	Y			Y				
Chemistry Lab Abnormalities of Potential Clinical Importance	Y			Y				
Haematology Lab Abnormalities of Potential Clinical Importance	Y			Y				
Urinalysis Data by Visit				Y				

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Hepatobiliary (Liver)								
Liver Monitoring/ Stopping Event Reporting	Y							
Time on Treatment before Liver Stopping Event	Y							
Summary of Liver Biopsy Details	Y							
Summary of Liver Imaging Results	Y							
Medical Conditions for Subjects with Liver Stopping Events				Y				
ECG's								
ECG Findings	Y							
Change from Baseline in ECG Values					Y			
Maximum QTc Values Post-Baseline Relative to Baseline by Category					Y			
Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category					Y			
All ECG Values for Subjects with a Value of Potential Clinical Importance				Y				
Mean (95% CI) Change from Baseline in QTc interval by Time and Treatment						Y		
Vital Signs								
Vital Signs	Y			Y	Y			
Vital Sign Data Outside Clinical Concern Range	Y							
Vital Sign Results by Maximum Grade Increase Post Baseline Relative to Baseline					Y			

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.2.2. Display Details

7.2.2.1. Adverse Event Safety Analyses

All adverse event (AE) data will be summarized, sorted by the system organ class and preferred term assigned by MedDRA version 20.0, and presented by treatment group. The following summaries will be provided:

- Adverse events overview
- All adverse events by SOC and PT and all adverse events by maximum grade and SOC and PT
- Drug related adverse events by SOC and PT and drug related adverse events by maximum grade and SOC and PT
- Serious adverse events
- Adverse events leading to withdrawal from study/permanent discontinuation of study treatment
- Common (>= 5%) adverse events by overall frequency
- Common (>= 5%) non-serious adverse events by overall frequency
- Cardiovascular adverse events of special interest

Cardiovascular AEs are defined as myocardial infarction/unstable angina, congestive heart failure, arrhythmias, valvulopathy, pulmonary hypertension, cerebrovascular events/stroke and transient ischemic attack, peripheral arterial thromboembolism, deep venous thrombosis/pulmonary embolism, and revascularization.

The following listings will be provided:

- All adverse events
- Subject numbers for individual AEs
- Drug related adverse events
- Serious adverse events
- Drug related serious adverse events
- Adverse events leading to withdrawal from study/permanent discontinuation of study treatment
- Fatal adverse events
- Non-fatal serious adverse events
- Cardiovascular adverse events of special interest

7.2.2.2. Clinical Laboratory Safety Analyses

Haematology and clinical chemistry parameters collected are listed below.

Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Haematology	Platelet Count	*RBC Indices:*	*WBC Count with Differential:*
	RBC Count	MCV	Neutrophils
	Haemoglobin	MCH	Lymphocytes with T-cell subsets
	Haematocrit		Monocytes
			Eosinophils
			Basophils
Clinical Chemistry	BUN	Potassium	AST (SGOT)
	Creatinine	Sodium	ALT (SGPT)
	Glucose	Bicarbonates	Alkaline phosphatise
	Troponin	Total and direct bilirubin	Total Protein
	Albumin		

Laboratory values, treatment emergent toxicities, and change from baseline for haematology, clinical chemistry, and liver function parameters will be summarized by visit and by treatment group. Laboratory values for haematology, clinical chemistry, liver function, and urinalysis will also be listed by subject. In addition, the number and percentage of subjects with on-treatment laboratory abnormalities worsened from baseline by maximum grade will be reported for haematology, clinical chemistry, and liver function parameters. The number and percentage of subjects with laboratory values of potential clinical importance will be summarized and listed (potential clinical importance criteria are specified in Section 12.8).

7.2.2.3. Other Safety Analyses

7.2.2.3.1. Electrocardiograms

A summary of the number and percentage of subjects who had abnormal and/or clinically significant ECG findings will be displayed by treatment. Additionally, summary statistics of change from baseline in ECG values will be presented. Maximum QTc values and maximum increase in QTc values post-baseline relate to baseline will be summarized by category. Mean (95% CI) change from baseline in QTcB-interval and QTcF interval will be plotted by time and treatment. All ECG Values for Subjects with a Value of Potential Clinical Importance will be listed (potential clinical importance criteria are specified in Section 12.8).

7.2.2.3.2. Vital Signs

Each vital sign parameter (systolic blood pressure, diastolic blood pressure, and heart rate) at every assessed time point will be summarised (n, mean, standard deviation,

median, minimum, and maximum). A summary of the number and percentages of vital sign changes by category (low, normal/no change, high) from baseline compared to those collected on Day 10 will be tabulated, and a summary of vital sign results by maximum grade increase post-baseline relative to baseline will be generated. A by-subject listing of vital signs for all subjects will be produced. A summary of the number and percentage of subjects who had vital signs outside the clinical concern range will be displayed by day, category, and treatment (potential clinical importance criteria are specified in Section 12.8).

7.2.2.3.3. Hepatobiliary (Liver)

Liver monitoring/stopping event reporting will be summarized by treatment group. A summary of time on treatment before liver stopping will be displayed. Listings of medical conditions for subjects with liver stopping events and of function lab abnormalities of potential clinical importance will also be produced.

7.3. Pharmacokinetic Analyses

7.3.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the PK Population for plasma PK concentrations, and PK Parameter Population for plasma PK parameters, unless otherwise specified.

Table 5 provides an overview of the planned analyses, with full details being presented in Appendix 12 List of Data Displays.

Table 5 Overview of Planned Pharmacokinetic Analyses

Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Plasma PK Concentrations				Y	Y[1] [2]	Y[1]	Y				Y	Y	Y	
Plasma PK Parameters	Y			Y	Y	Y	Y[3]	Y	Y		Y			

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Linear and Semi-Log plots will be created on the same display.
[2] Separate mean and median plots will be generated.
[3] Create as table using GSK listing standard.

7.3.2. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 12.5.3 Reporting Process & Standards).

7.3.3. Pharmacokinetic Parameters

7.3.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 12.5.3 Reporting Process & Standards).
- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin Version 6.4 or higher.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 6 will be determined from the plasma concentration-time data, as data permit.

Table 6 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
Day 1	
AUC(0-24)	Area under the concentration-time curve from time zero to the concentration at 24 hour post dose. AUC will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
C24	Concentration at 24 hours post dose
tmax	Time to reach Cmax, determined directly from the concentration-time data.
tlag	absorption lag time
Day 10	
AUC(0-τ)	Area under the concentration-time curve over the dosing interval. AUC will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
C0	Concentration at pre-dose
Cτ	Concentration at the end of the dosing interval
Cτ-avg	Defined as average of Days 8 -10 pre-dose concentration and Day 10 concentration at 24 hours
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
λz	The slope of the apparent terminal phase
Rsq	The correlation coefficient of the slope of the terminal phase
t½	Apparent terminal half-life will be calculated as: t½ = ln2 / λz
CL/F	Apparent oral clearance will be calculated as: CL/F = Dose / AUC(0- τ)
R_AUC	The accumulation ratio of AUC will be calculated as: will be calculated as: R_AUC = AUC(0-τ) Day 10 / AUC(0-24) Day 1
R_Cmax	The accumulation ratio of Cmax will be calculated as: will be calculated as: R_Cmax = Cmax Day 10 / Cmax Day 1
R_Cτ	The accumulation ratio of Cτ will be calculated as: will be calculated as: R_Cτ = Cτ Day 10 / C24 Day 1

NOTES:

- Additional parameters may be included as required.
- Lambda_z is the terminal phase rate constant.

7.3.3.2. Statistical Analysis of Pharmacokinetic Parameters

All the derived parameters described in Table 6 will be listed. For each of these parameters, except tmax, tmin, and tlag, the following summary statistics will be calculated for each active treatment group: median, maximum, minimum, arithmetic mean, standard deviation, coefficient of variation on arithmetic mean, geometric mean,

coefficient of variation on geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data. For tmax, tmin, and tlag, median, maximum, minimum, arithmetic mean and standard deviation will be calculated.

The following pharmacokinetic statistical analyses will only be performed, if sufficient data is available (i.e. if subjects have well defined plasma profiles).

Pharmacokinetic Statistical Analyses
Endpoint(s)
• Plasma primary PK endpoints include **Day 1**: area under the plasma concentration time curve AUC(0-24), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 24 hours post dose (C24), absorption lag time (tlag); **Day 10**: AUC(0-τ), pre-dose concentration (C0), concentration at end of dosing interval (Cτ), Cmax, tmax, t½, and apparent oral clearance (CL/F), if data permit
Model Specification
• To assess the dose proportionality of plasma GSK2838232, PK parameters from Day 1 [AUC(0-24), Cmax and C24] and Day 10 [AUC(0-τ), Cmax, and Cτ] will be assessed using a power model if multiple dose levels are assessed. The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. A fixed effects power model will be used. The mean slope will be estimated from the power model with the corresponding 90% CI, separately for Day 1 and Day 10. • To assess the achievement of steady state, pre-dose concentrations between Days 7-10 for each treatment. A linear mixed model using Day, Treatment, and Day by Treatment interaction as fixed effects and subject as a random effect on the ln-transformed pre-dose values will be performed evaluating whether steady state was achieved using Helmert transformation approach. The comparison will begin with Day 7 vs the average of Days 8, 9 and 10. The ratio of Geometric LS means and its 95% CI will be presented for the comparison(s).
Model Checking & Diagnostics
• Refer to Appendix 13: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Statistical analysis for dose proportionality from Day 1 [AUC(0-24), Cmax and C24], and Day 10 [AUC(0-τ), Cmax, and Cτ] will be presented in tabular format, respectively. The linear model will be used to provide a slope, intercept and a 90% CI of the slope. Example SAS Code: PROC MIXED; MODEL LNPKPARM=LNDOSE /SOLUTION CL ALPHA=0.1; ODS OUTPUT SOLUTIONF=SOLUTION1(RENAME=(ESTIMATE=EST STDERR=SE)); RUN; • Statistical analysis of steady state will be analyze using Helmert transformation approach Example SAS Code:

Pharmacokinetic Statistical Analyses

```
PROC MIXED DATA=PKPARM;
CLASS TREATMENT DAY SUBJECT;
MODEL LNPKPARM = TREATMENT DAY
    TREATMENT*DAY/DDFM=KR;
RANDOM SUBJECT;
LSMEANS TREATMENT*DAY;
ESTIMATE "Treatment A: DAY 7 VS AVERAGE OF DAYS 8 TO 10"
DAY 2 -1 -1 TREATMENT*DAY 2 -1 -1 0 0 0 0 0 0 0 0 0 /DIVISOR=2 CL ALPHA=.1;
ESTIMATE "Treatment B: DAY 7 VS AVERAGE OF DAYS 8 TO 10"
DAY 2 -1 -1 TREATMENT*DAY 0 0 0 2 -1 -1 0 0 0 0 0 0  /DIVISOR=2 CL ALPHA=.1;
ESTIMATE "Treatment C: DAY 7 VS AVERAGE OF DAYS 8 TO 10"
DAY 2 -1 -1 TREATMENT*DAY 0 0 0 0 0 0 2 -1 -1 0 0 0 /DIVISOR=2 CL ALPHA=.1;
ESTIMATE "Treatment D: DAY 7 VS AVERAGE OF DAYS 8 TO 10"
DAY 2 -1 -1 TREATMENT*DAY 0 0 0 0 0 0 0 0 0 0  2 -1 -1/DIVISOR=2 CL ALPHA=.1;
RUN;
```

8. PHARMACODYNAMIC ANALYSES

The dose-response model will be generated using subjects from the Per Protocol population. Relationships between dose and PD measures (e.g., Log10 reduction in plasma HIV-1 RNA to Day 11 from baseline, or maximum reduction in log10 plasma HIV-1 RNA from baseline) measures will be explored with an Emax and linear models. Model selection will be based on Akaike Information Criteria (AIC) value, where model with the lowest AIC value will be considered the best model.

Table 7 provides an overview of the planned analyses, with full details being presented in Appendix 12 List of Data Displays.

Table 7 Overview of Planned PD Analyses

	Absolute							Change from Baseline						
	Stats Analysis			Summary			Individual	Stats Analysis			Summary			Individual
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Pharmacodynamic Analyses														
Dose-Response Model											Y	Y		

NOTES:

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- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Primary Statistical Analyses: Dose Response Model

Endpoint

- Maximum decline in plasma HIV-1 RNA and CD4+ with Doses

Model Specification

- To model the dose-response relationship, a frequentist simplified Emax model is planned. This model assumes the following form:

$$\Delta BL = \frac{(Emax)}{1 + (\frac{ED50}{Dose})} + \epsilon$$

Where:

- ΔBL is the maximum change from baseline, defined as the viral load decline in Plasma HIV-1 RNA and the Day 11 change from baseline for CD4+
- Emax is the maximum response
- ED50 is the dose that attains the 50% of the maximal effect ε is a random error assumed to be normally distributed with mean zero and constant variance (σ^2)

The observed decline in Plasma HIV-1 RNA will be used as the response variable in the Emax model.

The derived data from this Emax model (estimates Emax, ED50 and Variance along with their standard error, and 95% CI) will be tabulated and a dose-response curve will also be produced.

If problems are encountered Emax model or if the Emax shape is a poor fit for the data and a linear relationship looks plausible across the dose range, then a linear model will be considered of the form:

$$\Delta Plasma = \alpha Dose$$

Model Checking & Diagnostics

- Refer to Appendix 13: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- The derived data from this Emax model (estimates Emax, EC50 and Variance along with their standard error, and 95% CI) will be tabulated and an exposure-response curve will also be produced.

  Example SAS Code:
  PROC NLMIXED;
  PARMS E0 = EST EMAX = EST ED50 = EST S2E = SE;
  BOUNDS E0>0 EMAX>0 ED50>0 S2E>0;
  PRED = E0 +(EMAX-E0)/(1+(ED50/DOSE));

Primary Statistical Analyses: Dose Response Model
MODEL RESPONSE ~ NORMAL (PRED, S2E); PREDICT PRED OUT=DOSE; RUN;

9. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

9.1. PK/PD Analyses of HIV-1 RNA

Scatter plots of plasma HIV-1 RNA change from baseline to Day 11 and maximum change from baseline vs. plasma GSK2838232 PK parameters on Day 10 [AUC(0-24), Cmax, C0, Cτ, and Cτ-avg [defined as average for Days 8 -10 pre-dose concentration, and Day 10 concentration at 24 hours] will be generated separately for each active treatment and overall. The Pearson's correlations between plasma HIV-1 RNA change from baseline to Day 11 and maximum change from baseline and plasma GSK2838232 PK parameters on Day 10 will be summarized by treatment and overall.

Relationships between various PK parameters (Day 10 AUC(0-τ), Day 10 Cmax, Day 10 C0, Cτ and Cτ-avg) and PD measures (Log10 reduction in plasma HIV-1 RNA to Day 11 from baseline, or maximum reduction in log10 plasma HIV-1 RNA from baseline) will be explored with various Emax models and graphically with Emax model results overlaid with the observed PK/PD values. Model selection will be based on Akaike Information Criteria (AIC) value, where model with the lowest AIC value will be considered the best model.

Table 8 Overview of Planned PK/PD Analyses

	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK/PD														
Emax Exposure-Response Model											Y	Y		

NOTES:

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Primary Statistical Analyses: Exposure Response Model

Endpoint

- Change from baseline to Day 11 and maximum decline in plasma HIV-1 RNA and CD4+ relative to the Day 10 PK parameters (AUC(0-τ), C0, Cmax, Cτ and Cτ-avg)

Model Specification

- To model the exposure-response relationship, a frequentist three-parameter Emax model is planned. This model assumes the following form

$$\Delta VL = E0 + \frac{Emax}{1 + (\frac{EC50}{C})} + \epsilon$$

Where:

- ΔVL is the maximum viral load decline or decline to Day 11 in plasma HIV-1 RNA
- E0 is the baseline response
- Emax is the maximum response
- EC50 is the corresponding exposure/PK parameter value that attains the 50% of the maximal effect
- C is the PK parameter
- ε is a random error assumed to be normally distributed with mean zero and constant variance (σ^2)

Model Checking & Diagnostics

- Refer to Appendix 13: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- The derived data from this Emax model (estimates E0, Emax, EC50 and Variance along with their standard error, and 95% CI) will be tabulated and an exposure-response curve will also be produced. If E0 turns out as not significant, the reduced Emax model without baseline E0 will be selected as the final model.

  Example SAS Code:

```
PROC NLMIXED;
PARMS E0 = EST EMAX = EST ED50 = EST S2E = SE;
BOUNDS E0>0 EMAX>0 ED50>0 S2E>0;
PRED = E0 +(EMAX-E0)/(1+(ED50/PARAM));
MODEL RESPONSE ~ NORMAL (PRED, S2E);
PREDICT PRED OUT=DOSE;
RUN;
```

9.2. Concentration-QTcF Analyses

For each ECG assessment, the individual subject's QTcF change from baseline will be calculated and will be merged with time-matched PK concentration values, when available. QTcF change from baseline (y-axis) will be plotted against the PK concentration data (x-axis) with a linear regression overlay.

Table 9 Overview of Concentration-QTcF Analyses

	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK/PD														
PK Concentration-QTcF Individual Plot													Y	

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
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- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

10. SECONDARY STATISTICAL ANALYSES

10.1. Efficacy Analyses

10.1.1. Overview of Planned Efficacy Analyses

Both the Per Protocol and Intent-To-Treat populations will be used for all efficacy analyses if there are subjects excluded from the Per Protocol population. If there are no exclusions, then the Intent-To-Treat population will be used for all efficacy analyses.

To assess the development of viral resistance over 10 days, genotypic and phenotypic analyses will be carried out. Details of the analyses will be provided in a separate clinical virology report.

Table 10 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 12 List of Data Displays.

Table 10 Overview of Planned Efficacy Analyses

	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Immunology														
Change from baseline (Day 1) in CD4+ cell count to Day 11							Y				Y			
Clinical Virology														
Viral genotypic data							Y							
Viral phenotypic data							Y							

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

10.1.1.1. Immunology

Change from baseline (Day 1) in CD4+ cell count to Day 11 will be listed by treatment group, subject, and assessment day and summarized by treatment and assessment day.

10.1.1.2. Clinical Virology

Viral genotypic and phenotypic data will be listed by treatment group, subject, and assessment day.

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12. APPENDICES

Section	Appendix
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Section 12.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
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Section 12.13	Appendix 13: Model Checking and Diagnostics for Statistical Analyses

12.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

12.1.1. Exclusions from Per Protocol Population

The following criteria define the major protocol deviations, which may lead to the exclusion of a subject from the per protocol (PP) population (refer to Section 4for population definitions). These are major deviations that are considered to affect interpretation of the primary endpoints (change from baseline in plasma HIV-1 RNA, safety and tolerability parameters, and PK parameters). Protocol deviations will be recorded in the eCRF. Potential protocol deviations listed below will be reviewed by the clinical team to establish whether subjects meeting these criteria should be excluded from the PP population. This review will occur before the clinical database has been locked for the final analysis.

Number	Exclusion Description
01	Inclusion/Exclusion criteria not met. • Subjects who deviate from any inclusion/exclusion criteria, as recorded in the eCRF.
02	Not withdrawn after meeting the following stopping criteria • Liver chemistry stopping criteria • QTc stopping criteria • Stopping criteria based on Adverse Event
03	Use of prohibited concomitant medications
04	Informed Consent • Study-specific assessments conducted prior to obtaining proper consent.
05	Study visits performed out of window • Consecutive subject study visits performed out of window • Multiple study visits performed out of window by various subjects (Trending)
06	Assessments performed out of window • ECGs not performed at protocol timepoint • PK samples completed out of window • Samples for HIV-1 RNA PCR out of window
07	Safety assessments not performed • Central safety lab samples not collected and/or not properly sent to Q2
08	Incorrect study treatment or non-compliance • Unresolved IP accountability discrepancy • IP storage guidelines not followed • IP incorrectly administered • IP accountability not done
09	Lack of PI oversight

12.2. Appendix 2: Time & Events

12.2.1. Protocol Defined Time & Events

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

Day:	Screen[1]	Random	1	2	3	4	5	6[2]	7	8	9	10	11	12	14±1	21±1 (FU)	ET
HIV-associated conditions assessment	X		X	X	X	X	X			X	X	X	X	X	X	X	X
PK blood sample[9]			X	X	X	X	X			X	X	X	X	X	X		X[14]
Plasma samples[10]	X		X										X				
Dosing[11]			X	X	X	X	X	X	X	X	X	X					
PGx[12]			X														
Telephone call to IVRS[14]	X	X															
Plasma for storage[15]			X	X	X	X	X			X	X	X	X	X	X	X	X
Outpatient visit	X			X	X	X	X			X	X		X	X	X	X	X

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

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

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

12.3. Appendix 3: Assessment Windows

12.3.1. Definitions of Assessment Windows for Analyses

Analyses will be presented by scheduled visits as collected in the CRF. The following table presents protocol defined assessment windows.

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Safety and Efficacy	All	14 - 21 days prior to first dose	21 days prior to first dose	14 days prior to first dose	SCREEN
Safety and Efficacy	All	Day 14	Day 13	Day 15	DAY14FUP
Safety	ECG	Day 4	Day 3	Day 5	DAY4
Safety	ECG	Day 8	Day 7	Day 9	DAY8

NOTES:

Screening visit window may be extended to 30 days upon discussion with the Medical Monitor (i.e., subject has scheduling conflicts or any screening assessment needs to be repeated).

12.4. Appendix 4: Treatment States and Phases

12.4.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to the start and/or stop date of the study treatment.

Treatment Phase	Definition
Screening Period	Day -30 to Day -1
Treatment Period	Day 1 to Day 10 / study treatment stop date
Follow-up Period	Study treatment stop date + 1 to Day 21 (±1 day)

12.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

12.4.2.1. Treatment States for Laboratory Data

Treatment State	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 1
Post-Treatment	Date > Study Treatment Stop Date +1

NOTES:

- If the study treatment stop date is missing then the assessment will be considered to be On-Treatment

12.4.2.2. Treatment States for AE Data

Treatment State	Definition
On-treatment	Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 12
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on CRF

NOTES:

- If the study treatment stop date is missing then the AE will be considered On-Treatment.

12.4.2.3. Classification of cardiovascular adverse events of special interest

Cardiovascular AEs of special interest will be determined through clinical team review of preferred terms for all captured adverse events.

12.4.2.4. Classification of prior, concomitant, or post-therapy medications

Prior medications are those taken (i.e., started) before the start date of study treatment. Concomitant medications are those taken (i.e., started or continued) at any time between the start date and stop date of study treatment, inclusive. Prior medications that were continued during the study treatment period are also considered as concomitant medications. Post-treatment medications are those started after the stop date of study treatment. Concomitant medications that were continued after the stop date of the study treatment are also considered as post-treatment medications.

It will be assumed that medication has been taken on the date in which it is reported as started or stopped. Also, for any medication starting on the same date as study treatment, it will be assumed that the medication was taken after the subject started taking the study treatment.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions		
RandAll NG	**Data Displays for Reporting[1]**	
Description	**Description**	**Order [2]**
GSK2838232 20 mg	20 mg GSK2838232/150 mg Cobicistat	1
Low-Dose 3	50 mg GSK2838232/150 mg Cobicistat	2
Mid-Dose 2	100 mg GSK2838232/150 mg Cobicistat	3
High-Dose 1	200 mg GSK2838232/150 mg Cobicistat	4

NOTES:

1. Unless otherwise indicated in data displays.
2. Order represents treatments being presented in TFL, as appropriate.

12.5.2. Baseline Definition & Derivations

12.5.2.1. Baseline Definitions

For all endpoints the baseline value will be the latest pre-dose assessment.

12.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Maximum Decline from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum decline

NOTES:

- Unless otherwise specified, the baseline definitions specified in Section 12.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

12.5.3. Reporting Process & Standards

Reporting Process
Software
• The currently supported versions of SAS software, version 9.2 or higher, will be used.
Analysis Datasets
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 &

Reporting Process
ADaM IG Version 1.1.) • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for SDTM.
Generation of RTF Files
• RTF files will be generated for Final Analysis TLFs.

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.	
Planned and Actual Time	
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported.

Reporting Standards	
	[1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data) [2] CV_w (%) = $\sqrt{}$ (exp(MSE) - 1) * 100 (MSE = mean square error from mixed effect model of loge-transformed data).
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Time Point
• Triplicate 12-lead ECGs will be recorded at each study-specified visit. Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two or more values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from treatment start date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Treatment Start Date → Study Day = Ref Date – Treatment Start Date
  • Ref Data ≥ Treatment Start Date → Study Day = Ref Date – (Treatment Start Date) + 1

Treatment Start Date
• The date of first dose of study treatment
Treatment Stop Date
• Calculated as the date of final dose of study treatment received. If treatment stop date is missing, then, for purposes of calculating exposure, it will be imputed using the date of last visit or the recorded date of withdrawal/completion, whichever is earlier. Note that the follow-up visit date must not be used as the date of last visit or recorded date of withdrawal/completion because this date will be off-treatment.
Study Completion/Withdrawal Date
• Date of withdrawal for subjects withdrawing (i.e., subjects who actively withdraw or are deemed lost to follow-up) from study or date of completion of study for subjects who complete the study, as documented in the eCRF.
Time Definitions (per GSK standard principles)
• 1 week = 7 days • 1 month = 30.4375 days • 1 year = 365.25 days

12.6.2. Study Population

Demographics
Age
Due to local privacy regulations, only the year of birth is recorded in the eCRF. The following algorithm will be used for imputation: • All dates of birth will be imputed using the 30th day of June. Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the subject will not be calculated and will remain missing. In listings of demographic data, the year of birth as entered will be displayed.
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)]^2**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were enrolled but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

12.6.3. Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as: [1] If QTcB is machine read & QTcF is not provided, then: $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.

ECG Parameters
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as: $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1

12.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) is defined as a subject who has completed all phases of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

12.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

12.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day and Non-missing End Date: If the day in a start date is missing, e.g. - -JUN2006, and the month is the one in which treatment started, assign the day to the day treatment started (i.e. the event is considered on-treatment as per Section 12.4.2) if treatment start date <= AE end date). Otherwise, set to the first of the month, 01JUN2006. ○ Missing Stop Day and Non-missing Start Date: Last day of the month (28th, 29th, 30th, or 31st as appropriate for the month and year) will be used. If the last day of the month is after the stop date of study treatment in the same month and treatment stop date >= AE start date, then study treatment stop date will be used. ○ Missing Start Day and Missing End Day: If both the day in a start date and

Element	Reporting Detail
	the day in an end date are missing, set them to the first day of the month and the last day of the month, respectively. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • The recorded partial date will be displayed in listings. Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

12.7.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

12.8. Appendix 8: Values of Potential Clinical Importance

12.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		30	
Bicarbonates	mmol/L		18	32
BUN	mmol/L			>9
Creatinine	µmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total Protein	g/L	Δ from ref. range	<15	>15
Troponin	ng/mL			≥0.01

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
Total Bilirubin	µmol/L	High	≥ 1.5xULN
Direct Bilirubin	µmol/L	High	>0.3x ULN

12.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
PR Interval	msec	< 120	> 200
QRS Duration	msec	< 60	> 109
QT Interval	msec	< 320	> 450
QTc Interval (Bazett)	msec	< 320	> 450
QTc Interval (Fridericia)	msec	< 320	> 450
RR Interval	msec	< 600	> 1200
Change from Baseline			
Increase from Baseline QTc	msec	> 60	

12.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Systolic Blood Pressure	mmHg	≥ 20	≥ 40	≥ 20	≥ 40
Diastolic Blood Pressure	mmHg	≥ 10	≥ 20	≥ 10	≥ 20
Heart Rate	bpm	≥ 15	≥ 30	≥ 15	≥ 30

12.8.4. Methods for Handling Centres

This study will be conducted in the United States and Canada. Data will be summarized for all centres combined. Statistical analyses will not be adjusted for centre.

12.9. Appendix 9: Population Pharmacokinetic Analyses

12.9.1. Blood Sample Collection

Blood samples for analysis of GSK2838232 concentrations will be collected at the time points indicated in Time and Events Tables (Appendix 2).

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

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

12.9.2. Sample Analysis

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

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

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

12.10. Appendix 10: Pharmacodynamic / Biomarker Analyses

12.10.1. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide plasma for viral genotype and phenotype analysis, at the times listed in the Time and Events Table in Appendix 2. Details concerning the handling, labelling and shipping of these samples will be supplied separately.

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

12.10.2. Genetics

Information regarding genetic research is included in Appendix 4, Section 12.4 of protocol amendment 3 (Dated: 15/JUN/2017).

12.10.3. Value Evidence and Outcomes

Not required.

12.11. Appendix 11 – Abbreviations & Trade Marks

12.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
AIDS	Auto immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AUC(0-τ)	Area under the plasma concentration time curve over the dosing interval
AUC(0-24)	Area under the plasma concentration time curve from time zero to the concentration at 24 hours post dose
A&R	Analysis and Reporting
Bpm	beats per minute
BIL	Bilirubin
C0	Concentration at pre-dose
Cτ	Concentration at the end of the dosing interval
Cτ-avg	Defined as average of Days 8 -10 pre-dose concentration, and Day 10 concentration at 24 hours
C24	Concentration at 24 hours post dose
CDISC	Clinical Data Interchange Standards Consortium
CL/F	Apparent oral clearance
CI	Confidence Interval
Cmax	Maximum observed concentration
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-To-Treat
g	gram
GSK	GlaxoSmithKline
GUI	Guidance
H	Hour(s)
HIV	Human Immunodeficiency Virus

Abbreviation	Description
Kg	Kilogram
λz	The slope of the apparent terminal phase
L	Litre
LOC	Last Observation Carries Forward
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mg	milligrams
MMRM	Mixed Model Repeated Measures
ng/mL	Nanogram per millilitre
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
R_AUC	The accumulation ratio of AUC from Day 10 to Day 1
R_Cmax	The accumulation ratio of Cmax from Day 10 to Day 1
R_Cτ	The accumulation ratio of Cτ from Day 10 to Day 1
RAP	Reporting & Analysis Plan
Rsq	The correlation coefficient of the slope of the terminal phase
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operation Procedure
t½	Apparent terminal half-life
tlag	Absorption lag time
tmax	Time to reach Cmax
TFL	Tables, Figures & Listings
U	Units

12.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
Phoenix WinNonlin
SAS
Tybost (cobicistat)

12.12. Appendix 12: List of Data Displays

12.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.22	
Efficacy	2.1 to 2.12	2.1 to 2.2
Safety	3.1 to 3.37	3.1
Pharmacokinetic	4.1 to 4.7	4.1 to 4.7
Pharmacodynamic	5.1	5.1 to 5.2
Pharmacokinetic / Pharmacodynamic	6.1	6.1 to 6.5
Section	**Listings**	
ICH Listings	1 to 20	
Non-ICH Listings	21 to 51	

12.12.2. Deliverable [Priority]

Delivery [Priority] [1]	Description
IB	Investigator's Brochure
SAC	Final Statistical Analysis Complete

NOTES:
1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

12.12.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Populations Analysed					
1.1.	All Screened	SP1	Summary of Study Populations		SAC
1.2.	ITT	NS1	Summary of Number of Subjects by Centre		SAC
Subject Disposition					
1.3.	ITT	ES1	Summary of Subject Disposition		IB, SAC
1.4.	All Screened	ES6	Summary of Reasons Screening Status and for Screen Failure		SAC
1.5.	Safety	SD1	Summary of Study Treatment Discontinuation	Use the primary reasons and the sub-reasons for IP discontinuation collected from the eCRF.	SAC
1.6.	ITT		Summary of Subjects at Each Visit		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demography & Disease Characteristics at Screening					
1.7.	ITT	DM1	Summary of Demographic Characteristics	Age, sex, child-bearing potential, race, ethnicity, height, weight, Baseline CDC HIV-1 Classification, and BMI. For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.1 Summary of Demographic Characteristics	IB, SAC
1.8.	ITT	DM11	Summary of Age Ranges		SAC
1.9.	ITT	DM5	Summary of Race & Racial Combinations	For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.2 Summary of Race and Racial Combinations	SAC
1.10.	ITT	DM6	Summary of Race & Racial Combinations Details	For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.2 Summary of Race and Racial Combinations	SAC
1.11.	Safety	FH1	Summary of Family History of Cardiovascular Risk		SAC
1.12.	Safety	SU1	Summary of Substance Use		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Protocol Deviations					
1.13.	ITT	DV1A	Summary of Protocol Deviations	See RAP Section 12.1.1 for categories of protocol deviations.	SAC
1.14.	ITT	DV1A	Summary of Deviations Leading to Exclusions from Per Protocol Population	See RAP Section 12.1.1 for categories of protocol deviations.	SAC
1.15.	ITT	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
Medical Condition & Concomitant Medications					
1.16.	Safety	MH1	Summary of Cardiovascular Medical Conditions		SAC
1.17.	Safety	MH1	Summary of Past Medical Conditions	Categories of medical conditions will be sorted in descending order of "Total" incidence, and medical conditions within each category will be sorted in descending order of "Total" incidence. If the "Total" incidence for any two or more medical conditions is equal, then they will be presented in alphabetical order.	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.18.	Safety	MH1	Summary of Current Medical Conditions	Categories of medical conditions will be sorted in descending order of "Total" incidence, and medical conditions within each category will be sorted in descending order of "Total" incidence. If the "Total" incidence for any two or more medical conditions is equal, then they will be presented in alphabetical order.	SAC
1.19.	Safety	CM1	Summary of Concomitant Medication ATC Level 1 by Ingredient	Medications will be sorted in descending order of "Total" incidence for the ATC level 1 and in descending order of total incidence for the ingredient within each ATC level. If the total incidence of for any two or more ingredients is equal, the events will be presented in alphabetical order. See GSK IDSL "CONCOMITANT MEDICATIONS STATISTICAL DISPLAY STANDARDS" (Version 12), Section 1.1.1	SAC
1.20.	Safety	CM1	Summary of Prior Medication ATC Level 1 by Ingredient		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
1.21.	Safety	COMP1	Summary of Study Treatment Overall Compliance		SAC
1.22.	Safety	EX1	Summary of Exposure to Study Treatment		IB, SAC

12.12.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Viral Load					
2.1.	ITT		Summary of Plasma HIV-1 RNA		SAC
2.2.	ITT		Summary of Change from Baseline to Day 11 and Maximum Decline from Baseline in Plasma HIV-1 RNA		SAC
2.3.	ITT		Summary of Modelled Plasma HIV-1 RNA Mean Rate of Decline and Maximum Decline by Treatment		SAC
2.4.	ITT		Summary of Proportion of Subjects with Plasma HIV-1 RNA <400 and < 50 copies/mL		SAC
2.5.	ITT		Summary of Proportion of Subjects with Plasma HIV-1 RNA Change from Baseline >1.5 log10 copies/mL Decrease		SAC
2.6.	PP		Summary of Plasma HIV-1 RNA	To be generated if there are subjects excluded from the Per Protocol population	SAC
2.7.	PP		Summary of Change from Baseline to Day 11 and Maximum Decline from Baseline in plasma HIV-1 RNA	To be generated if there are subjects excluded from the Per Protocol population	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	PP		Summary of Modelled Plasma HIV-1 RNA Mean Rate of Decline and Maximum Decline by Treatment	To be generated if there are subjects excluded from the Per Protocol population	SAC
2.9.	PP		Summary of Proportion of Subjects with Plasma HIV-1 RNA <400 and < 50 copies/mL	To be generated if there are subjects excluded from the Per Protocol population	SAC
2.10.	PP		Summary of Proportion of Subjects with Plasma HIV-1 RNA Change from Baseline >1.5 log10 copies/mL Decrease	To be generated if there are subjects excluded from the Per Protocol population	SAC
Immunology					
2.11.	ITT		Summary of Change from Baseline (Day 1) in CD4+ Cell Count to Day 11		SAC
2.12.	PP		Summary of Change from Baseline (Day 1) in CD4+ Cell Count to Day 11	To be generated if there are subjects excluded from the Per Protocol population	SAC

12.12.5. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Viral Load					
2.1.	ITT		Plot of Mean and Median Change from Baseline (Day 1) in Plasma HIV-1 RNA by Treatment		SAC
2.2.	PP		Plot of Mean and Median Change from Baseline (Day 1) in Plasma HIV-1 RNA by Treatment	To be generated if there are subjects excluded from the Per Protocol population	SAC

12.12.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE13	Adverse Events Overview		SAC
3.2.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term		IB, SAC
3.3.	Safety	AE5B	Summary of All Adverse Events by System Organ Class and Preferred Term and Maximum Grade		SAC
3.4.	Safety	AE5B	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade		SAC
3.5.	Safety	AE1	Summary of Serious Adverse Events by System Organ Class and Preferred Term		SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6.	Safety	AE1	Summary of Drug Related Adverse Events by System Organ Class and Preferred Term		IB, SAC
3.7.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study		SAC
3.8.	Safety	AE1	Summary of Common (>=5%) Adverse Events By Overall Frequency		SAC
3.9.	Safety	AE1	Summary of Common (>=5%) Non-Serious Adverse Events By Overall Frequency		SAC
3.10.	Safety	AE1	Summary of Cardiovascular Adverse Events of Special Interest		SAC
Laboratory Values					
3.11.	Safety	LB1	Summary of Clinical Chemistry Data by Visit		SAC
3.12.	Safety	LB1	Summary of Change from Baseline in Clinical Chemistry Data by Visit		SAC
3.13.	Safety	LB1	Summary of Haematology Data by Visit		SAC
3.14.	Safety	LB1	Summary of Change from Baseline in Haematology Data by Visit		SAC
3.15.	Safety	LB1	Summary of Liver Function Data by Visit		SAC
3.16.	Safety	LB1	Summary of Change from Baseline in Liver Function by Visit		SAC
3.17.	Safety		Summary of Treatment Emergent Clinical Chemistry Toxicities		SAC
3.18.	Safety	LB2	Summary of On-Treatment Laboratory Abnormalities Worsened from Baseline by Maximum Grade – Chemistry		IB, SAC
3.19.	Safety		Summary of Treatment Emergent Haematology Toxicities		SAC
3.20.	Safety	LB2	Summary of On-Treatment Laboratory Abnormalities Worsened from Baseline by Maximum Grade – Haematology		IB, SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.21.	Safety		Summary of Treatment Emergent Liver Toxicities		SAC
3.22.	Safety	LB2	Summary of On-Treatment Laboratory Abnormalities Worsened from Baseline by Maximum Grade – Liver Function		IB, SAC
3.23.	Safety	LB2	Summary of Chemistry Laboratory Abnormalities of Potential Clinical Importance		SAC
3.24.	Safety	LB2	Summary of Haematology Laboratory Abnormalities of Potential Clinical Importance		SAC
3.25.	Safety	LB2	Summary of Liver Function Laboratory Abnormalities of Potential Clinical Importance		SAC
Hepatobiliary (Liver)					
3.26.	Safety	Liver1	Summary of Liver Monitoring/Stopping Event Reporting		IB, SAC
3.27.	Safety	Liver2	Summary of Time on Treatment Before Liver Stopping Event		IB, SAC
3.28.	Safety	Liver3	Summary of Liver Biopsy Details		SAC
3.29.	Safety	Liver4	Summary of Liver Imaging Details		SAC
ECGs					
3.30.	Safety	EG1	Summary of ECG Findings		IB, SAC
3.31.	Safety	EG2	Summary of Change from Baseline in ECG Values		SAC
3.32.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.33.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.34.	Safety	VS1	Summary of Vital Sign Values by Visit		SAC
3.35.	Safety	VS3	Summary of Worst Case Vital Sign Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC
3.36.	Safety	VS2	Summary of Vital Sign Data Outside Clinical Concern Range		SAC
3.37.	Safety	VS6	Summary of Vital Sign Results by Maximum Grade Increase Post Baseline Relative to Baseline		SAC

12.12.7. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
3.1.	Safety		Mean (95% CI) Change from Baseline in QTc interval by Time and Treatment		SAC

12.12.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	PK	PK01	Summary of Plasma GSK2838232 Pharmacokinetic Concentration-Time Data		SAC
PK Derived Parameters					
4.2.	PK	PKPL1P	Listing of Derived Plasma GSK2838232 Pharmacokinetic Parameters by Treatment - Day 1	Parameters with units	SAC
4.3.	PK	PKPL1P	Listing of Derived Plasma GSK2838232 Pharmacokinetic Parameters by Treatment – Day 10	Parameters with units	SAC
4.4.	PK	PKPT2	Summary Statistics of Derived Plasma GSK2838232 Pharmacokinetic Parameters by Treatment and Day	Parameters with units	SAC
4.5.	PK	PKPT4	Summary Statistics of Log-Transformed Derived Plasma GSK2838232 Pharmacokinetic Parameters and Day	Parameters with units	SAC
4.6.	PK		Assessment of Dose Proportionality of GSK2838232 by Day	Day 1 parameters: AUC(0-24) and Cmax Day 10 parameters: AUC(0-τ) and Cmax	SAC
4.7.	PK		Assessment of Plasma GSK2838232 Steady State Concentrations	Pre-dose concentration values for Day 7, 8, 9 and 10	SAC

12.12.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
4.1.	PK	PKCF1P	Individual Plasma GSK2838232 Concentration-Time Plot by Day (Linear and Semi-Log)	Present individual Day 1 and Day 10 profile on same plot. Paginate by Subject	SAC
4.2.	PK	PK26	Individual Plasma GSK2838232 Trough Concentration-Time Plot (Linear and Semi-Log)	Present Pre-dose and 24 hr time points only. Paginate by Subject	SAC
Mean/Median Concentration Plots					
4.3.	PK	PKCF2	Mean Plasma GSK2838232 Concentration-Time Plots by Treatment and Day (Linear and Semi-Log)	Paginate by Day	SAC
4.4.	PK	PK27	Mean Plasma GSK2838232 Trough Concentration-Time Plots by Treatment (Linear and Semi-Log)	Pre-dose and 24 hr time points only. Time scale by Day	SAC
4.5.	PK	PKCF3	Median Plasma GSK2838232 Concentration-Time Plots by Treatment and Day (Linear and Semi-Log)	Paginate by Day	SAC
4.6.	PK	PK27	Median Plasma GSK2838232 Trough Concentration-Time Plots by Treatment (Linear and Semi-Log)	Pre-dose and 24 hr time points only. Time scale by Day	SAC
PK Parameter Plots					
4.7.	PK	PK28	Individual and Geometric Mean (95% CI) of Plasma PK Parameters versus Dose by Day	Paginate by Parameter and Day. Present overlay of individual parameters with Geometric mean and 95%CI for parameters and results for Table 4.4 for regression line	SAC

12.12.10. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PD Linear and Emax Models					
5.1	PP		Summary of Estimates from Dose-Response Model	Note that max decline from baseline is the endpoint for this analysis. To be generated using those subjects in the PP population	SAC

12.12.11. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK/PD – RNA Change from Baseline					
5.1	PP		Scatter Plot of HIV RNA Maximum Decline from Baseline versus Dose		SAC
5.2	PP	PK28	Scatter Plot of Day 11 CD4+ Change from Baseline versus Dose		SAC

12.12.12. Pharmacokinetic / Pharmacodynamic Tables

Pharmacokinetic/Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
6.1	PK/PD	PK28	Summary of Estimates from Exposure Response Model	Note that max decline from baseline is the endpoint for this analysis. To be generated using those subjects in the PK/PD population	SAC

12.12.13. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK/PD – RNA Change from Baseline					
6.1.	PK/PD	PK28	Scatter Plot of Day 11 HIV RNA Change from Baseline versus Day 10 Plasma PK Parameters	Present Day 11 CFB HIV RNA vs Day 10 AUC(0-τ) and Cmax	SAC
6.2.	PK/PD	PK28	Scatter Plot of HIV RNA Maximum Change from Baseline versus Day 10 Plasma PK Parameters	Maximum CFB HIV RNA vs Day 10 AUC(0-τ) and Cmax	SAC
PK/PD – CD4+ Change from Baseline					
6.3.	PK/PD	PK28	Scatter Plot of Day 11 CD4+ Change from Baseline versus Day 10 Plasma PK Parameters	Present Day 11 CFB CD4+ vs Day 10 AUC(0-τ) and Cmax	SAC
6.4.	PK/PD	PK28	Scatter Plot of CD4+ Maximum Change from Baseline versus Day 10 Plasma PK Parameters	Maximum CFB CD4+ vs Day 10 AUC(0-τ) and Cmax	SAC

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK/PD – QTcF Change from Baseline					
6.5.	PK/PD	PK28	Scatter Plot of QTcF Change from Baseline versus Time-matched PK Concentration		SAC

12.12.14. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Populations Analysed					
1.	ITT		Listing of Subjects Excluded from Any Population		SAC
Subject Disposition					
2.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
3.	ITT	ES2	Listing of Reasons for Study Withdrawal		IB, SAC
4.	ITT		Listing of Planned and Actual Treatment Assignment		SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demography & Disease Characteristics at Screening					
5.	ITT	DM2	Listing of Demographic Characteristics	Age, sex, race, ethnicity, height, weight, and BMI. For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.1 Summary of Demographic Characteristics	SAC
6.	ITT	DM9	Listing of Race & Racial Combinations	For details on Race categories shown in this table, please see GSK IDSL Demography Statistical Display Standards, Section 1.1.2 Summary of Race and Racial Combinations	SAC
Protocol Deviations					
7.	ITT		Listing of Protocol Deviations	See RAP Section 12.1.1 for categories of protocol deviations.	SAC
8.	ITT	IE3	Listing of Inclusion/Exclusion Criteria Deviations		SAC
Exposure and Treatment Compliance					
9.	Safety	OEX8B	Listing of Extent of Exposure to Study Treatment		IB, SAC
Adverse Events					
10.	Safety	AE8	Listing of All Adverse Events		IB, SAC
11.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
12.	Safety	AE8	Listing of Serious Adverse Events		IB, SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
13.	Safety	AE8	Listing of Drug Related Serious Adverse Events		IB, SAC
14.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study/Permanent Discontinuation of Study Treatment		IB, SAC
15.	Safety	AE8	Listing of Fatal Adverse Events		IB, SAC
16.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events		SAC
17.	Safety	AE8	Listing of Cardiovascular Adverse Events of Special Interest		SAC
Laboratory Values					
18.	Safety	LB5	Listing of Chemistry Laboratory Abnormalities of Potential Clinical Importance		SAC
19.	Safety	LB5	Listing of Haematology Laboratory Abnormalities of Potential Clinical Importance		SAC
20.	Safety	LB5	Listing of Liver Function Laboratory Abnormalities of Potential Clinical Importance		SAC

12.12.15. Non-ICH Listings

Non-ICH:: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Populations Analysed					
21.	All Screened		Listing of Study Populations		SAC

Non-ICH:: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
22.	All Screened	ES7	Listing of Reasons for Screen Failure		SAC
Demography & Disease Characteristics at Screening					
23.	ITT		Listing of Cardiovascular Risk Assessment		SAC
24.	ITT		Listing of HIV Risk Factors		SAC
Medical Condition & Concomitant Medications					
25.	Safety		Listing of Cardiovascular Events		SAC
26.	ITT	MH2	Listing of Medical Conditions (Current/Past)		SAC
27.	ITT	CM2	Listing of Concomitant Medication ATC Level 1 by Ingredient	See GSK IDSL "CONCOMITANT MEDICATIONS STATISTICAL DISPLAY STANDARDS" (Version 12), Section 1.1.1	SAC
28.	ITT	CM2	Listing of Prior Medication ATC Level 1 by Ingredient		SAC
29.	ITT	CM6	Listing Relationship Between ATC Level 1, Ingredients And Verbatim Text		SAC
30.	ITT		Listing of HIV Associated Conditions		SAC
Efficacy					
31.	ITT		Listing of Plasma HIV-1 RNA		SAC
32.	ITT		Listing of Change from baseline (Day 1) in CD4+ cell count to Day 11		SAC
33.	ITT		Listing of Viral Genotypic Data		SAC
34.	ITT		Listing of Viral Phenotypic Data		SAC

Non-ICH:: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
35.	Safety	AE8	Listing of Drug Related Adverse Events		IB, SAC
Laboratory Values					
36.	Safety	LB5	Listing of Clinical Chemistry Data		IB, SAC
37.	Safety	LB5	Listing of Haematology Data		IB, SAC
38.	Safety	LB5	Listing of Liver Function Data		IB, SAC
39.	Safety	LB5	Listing of Urinalysis Data		SAC
Hepatobiliary (Liver)					
40.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
ECGs					
41.	Safety	EG3	Listing of All ECG Values for Subjects with a Value of Potential Clinical Importance		IB, SAC
Vital Signs					
42.	Safety	VS4	Listing of Vital Sign Values by Visit		SAC
Pharmacokinetic					
43.	PK	PKCL1P	Listing of Plasma GSK2838232 Concentrations (ng/mL) by Treatment	List all the concentration data including unscheduled. Repeat for all treatments.	SAC

Non-ICH:: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Statistical Output					
44.	ITT		Statistical Output Listing of Modelled Plasma HIV-1 RNA Mean Rate of Decline by Treatment		SAC
45.	ITT		Statistical Output Listing of Modelled Plasma HIV-1 RNA Maximum Decline by Treatment		SAC
46.	PP		Statistical Output Listing of Modelled Plasma HIV-1 RNA Mean Rate of Decline by Treatment		SAC
47.	PP		Statistical Output Listing of Modelled Plasma HIV-1 RNA Maximum Decline by Treatment		SAC
48.	PK		Statistical Output Listing of Assessment of Dose Proportionality of GSK2838232 by Day		SAC
49.	PK		Statistical Output Listing of Assessment of Plasma GSK2838232 Steady State Concentrations		SAC
50.	PP		Statistical Output Listing of Summary of Estimates from Dose-Response Model		SAC
51.	PK/PD		Statistical Output Listing of Summary of Estimates from Exposure Response Model		SAC

12.13. Appendix 13: Model Checking and Diagnostics for Statistical Analyses

12.13.1. Statistical Analysis Assumptions

Endpoint(s)	• PK endpoints AUC(0-∞), AUC(0-τ) and Cmax
Analysis	• Mixed Effects
Assumptions: • Model assumptions will be applied, but appropriate adjustments may be made based on the data. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.	

Endpoint(s)	• PD dose response endpoints Emax, E0, ED50
Analysis	• Nonlinear Mixed Effects
Assumptions: • Model assumptions will be applied, but appropriate adjustments may be made based on the data.	

Endpoint(s)	• PKPD exposure response endpoints Emax, E0, EC50
Analysis	• Nonlinear Mixed Effects
Assumptions: • Model assumptions will be applied, but appropriate adjustments may be made based on the data.	