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

Title	:	Reporting and Analysis Plan for A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of GSK3732394 in Healthy Participants
Compound Number	:	GSK3732394
Effective Date	:	04-MAY-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Synoptic Clinical Study Report for Protocol 207863.
- This RAP is intended to describe the safety, tolerability, pharmacokinetic, and pharmacodynamic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Part 1 (Single Ascending Dose) Statistical Analysis Complete (SAC) deliverable. Due to early termination of the study only the first 3 cohorts were completed. This document will only include the reporting plan for subjects enrolled in the study.
- Only the primary and secondary endpoints are to be analysed due to the early termination.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 207863:

Revision Chronology:		
Original Protocol, DNG 2017N341355_00	11-APR-2019	Original
Amendment 01, DNG 2017N341355_01	06-JUN-2019	This amendment results from FDA "Study May Proceed" letter for IND Opening (Number 131394, Reference ID 4441322) dated 31-MAY-2019. FDA requested 9 clinical changes to the protocol.
Amendment 02, DNG 2017N341355_02	02-JUL-2019	This amendment results from a consensus between the Sponsor and the Study Site, that a confirmation of CD4+ T-cell count and CD4 percent values in healthy individuals with values within the normal range at screening, to be unnecessary. The removal of this confirmatory test is not determined to have effect on the evaluation of participant safety by the Sponsor or Study Site.
Amendment 03, DNG 2017N341355_03	12-SEP-2019	This amendment is based on 3 criteria. 1) Initial dose escalation data following completion of Cohort 1 indicated that Cohort 6 in the study design will be required. Flexible language to this affect has been removed. 2) Initial dose escalation data following completion of Cohort 1 indicate that anti-drug antibodies (ADA) have the potential to appear earlier than indicated pre-clinically. Day 7 and Day 10 collection of samples for ADAs have been added in Part 1 and for Day 8 in Part 2. 3) The previous consensus between the Sponsor and the Study Site on CD4+ T-cell count and CD4 percent values screening values under Amendment 02, requires further clarification.

All data displays (Tables, Figures & Listings) will use the term "Subject" which reflects CDISC and GSK Data Display Standards terminology.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• No changes or deviations specified in protocol amendment 3.	• No Statistical Analysis or outputs to be generated for Part 2 (Multiple Ascending Dose) or exploratory objectives/endpoints	• Study terminated prior to multiple dosing
• Full CSR	• Synoptic CSR	• Early study termination during Part 1 for non-safety reasons.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the safety and tolerability of single and multiple doses of GSK3732394 in healthy participants.	• GSK3732394 safety parameters: adverse events; post-baseline values and changes over time of clinical laboratory evaluations (haematology, clinical chemistry, urinalysis), vital signs, and ECG parameters from predose values
Secondary Objectives	**Secondary Endpoints**
• To describe the pharmacokinetic (PK) profile of single and multiple doses of GSK3732394 in healthy participants.	• Derived PK parameters for GSK3732394, as data allow: Part 1 (single dose): $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, T_{max}, t_{lag}, C_{last}, t_{last}, $t_{1/2}$, CL/F Part 2 (Repeated Once Weekly [QW] dosing): First week: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, t_{max}, t_{lag} • Last week: $AUC_{(0-\tau)}$, C_{max}, t_{max}, C_{trough}, $t_{1/2}$, CL/F.
• To examine dose proportionality following single and multiple doses of GSK3732394, as data allow.	• PK linearity assessment using derived PK parameters, as data allow: Part 1 (single dose): $AUC_{(0-\infty)}$, C_{max} • Part 2 (Repeat QW dosing): $AUC_{(0-\tau)}$, C_{max}, C_{τ}.
• To assess accumulation of GSK3732394 after multiple doses, as data allow.	• Accumulation indices for PK parameters assessed across first and last doses of multiple dosing, as data allow: $RAUC_{(0-\tau)}$, RC_{max}, RC_{τ}.
• To characterise CD4 receptor occupancy (RO) profile of single and multiple doses of GSK3732394.	• Percent of CD4 RO.
• To investigate the relationship	• C_{max}, C_{trough}, %RO

Objectives	Endpoints
between GSK3732394 exposures and CD4 RO.	
• To characterise potential immunologic impact on, and immune responses to, healthy participants who receive a single or multiple dose(s) of GSK3732394.	• Change from baseline in CD3/CD4/CD8 and activated T-cell counts and percentages. • Change from baseline in CD4 mean fluorescence intensity (MFI). • Titers and incidence of anti-GSK3732394 antibodies.
Exploratory Objectives	**Exploratory Endpoints**
• To model the relationship between GSK3732394 exposures and CD4 RO.	• Estimating parameters descriptive of the relationship including Concentration resulting in 50% RO (EC50), as data allow.
• To explore the correlation between GSK3732394 exposure and observed safety outcomes.	• Occurrence of AEs /laboratory abnormalities and corresponding plasma concentrations / doses of GSK3732394.
• To explore serum and urine metabolite(s) investigations of GSK3732394.	• Identification of any compound-related degradants

2.3. Study Design

Overview of Study Design and Key Features

Schematic:

PART 1 (6 GSK3732394 : 2 PBO)	SAD Cohort 1 (n = 8)	SAD Cohort 2 (n = 8)	SAD Cohort 3 (n = 8)	SAD Cohort 4 (n = 8)	SAD Cohort 5 (n = 8)	SAD Cohort 6[1] (n = 8)
Single SC Dose (C_{trough} RO)	10mg (<10%)	40mg (≤25%)	130mg (≤70%)	350mg (≤90%)	600mg (≤95%)	Up to 800mg or to repeat a prior dose

PART 2 (6 GSK3732394 : 2 PBO)	MAD Cohort 1 (n = 8)	MAD Cohort 2 (n = 8)	MAD Cohort 3 (n = 8)
4 Subcutaneous Doses (C_{trough} RO) Administered Once Weekly (QW)	130mg (<70%)	400mg (≤90%)	600mg (≤95%)

[1] An additional cohort (6) of up to 800mg or to repeat a prior dose may be included.

Note: Doses shown in schematic are nominal and intended to demonstrate general concepts relating to factors of escalation as a base case. Dose escalation in Part 1 will be based on target receptor occupancy/exposure and governed by safety and PK stopping criteria. Transition to Part 2 will be after the completion of dosing and evaluation of SAD Cohort 4 participants and after the predicted exposure of the starting MAD dose is within that observed with SAD dosing – maximum predicted AUC, C_{max} not exceeding the average maximum observed in evaluated SAD cohorts. (QW = once every week.).

Design Features	• 2 Part, double-blind (sponsor-unblinded), randomized, placebo-controlled, single and multiple-ascending-dose study. • In Part 1, a sufficient number of healthy adults will be screened to provide approximately 8 participants for randomization within each of the SAD dosing cohorts. Overall, up to approximately 48 participants will be included depending on the number of cohorts required. • In Part 2, a sufficient number of healthy adults will be screened to provide approximately 8 participants for randomization within each of the 3 MAD dosing cohort. Overall, up to approximately 24 participants will be included depending on the number of cohorts required.
Dosing	• In Part 1, the proposed dosing schedule is designed to investigate SAD of GSK3732394 in healthy participants. All doses will be administered subcutaneously. The SAD portion of the study will be conducted in at least five, but no more than six, separate cohorts of approximately eight healthy adult participants each. Each of the participants in the SAD cohorts will receive a single dose of blinded GSK3732394 or blinded PBO (GSK3732394 : PBO = 6:2, per their randomization assignment). Details of the starting dose and dose escalation can be found in Section 5.5.1 and Section 5.5.2, respectively, of the protocol. Dose escalation decisions, including the determination of subsequent doses in Part 1, will be determined by the Safety and Dose Escalation Committee (SDEC). See Section 5.5.5 of the protocol. • In Part 2, the proposed dosing schedule is designed to investigate multiple ascending doses (MAD) of GSK3732394 in healthy participants administered weekly for a total of four doses. All doses will be administered subcutaneously. • Part 2 consists of up to three ascending repeat-dose cohorts (MAD Cohorts 1, 2, and 3), each with approximately 8 participants (GSK3732394 : PBO = 6:2) who will receive four weekly doses of GSK3732394 or PBO on Days 1, 8, 15, and 22. Details of starting dose and dose escalations in Part 2 (MAD) can be

Overview of Study Design and Key Features	
	found in Section 5.5.3 of the protocol.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• In Part 1, participants will receive a single dose of GSK3732394 or PBO (6:2) on Day 1. Safety, PK and PD assessments will be performed at timepoints specified in the schedule of activity (SOA). Participants will remain in the clinic until the completion of the Day 14 procedures and will return to the clinic on Days 17, 21, and 24 for follow-up assessments, and an end-of-study evaluation on Day 28. • In Part 2, participants will receive doses of GSK3732394 or PBO (6:2) given at anticipated weekly intervals. Participants will remain in the clinic until the completion of the Day 35 procedures and will return to the clinic on Days 39, 42 and 46 for follow-up assessments, and an end-of-study evaluation on Day 49. Duration of participation through follow-up may be longer if actual PK parameters differ significantly from predicted values (e.g. if half-life is significantly longer than the predicted); but will not exceed five half-lives.
Interim Analysis	• No formal interim analyses (IA) are planned for this study. However, safety, tolerability, PK, and PD data will be reviewed before each dose escalation in Part 1 (single dose), Part 2 (repeat dose) and prior to MAD transition which will occur after at least the first 4 SAD cohorts.

2.4. Statistical Analyses

The main purpose of this study is to assess the safety, tolerability, and pharmacokinetic/pharmacodynamic attributes of subcutaneous doses of GSK3732394 in healthy participants. No formal hypotheses will be tested. Results will be descriptive in nature. Statistical modelling on select pharmacokinetic parameters will be performed to estimate dose proportionality. Point estimates with 90% confidence intervals will be reported, as appropriate.

3. PLANNED ANALYSES

3.1. Interim Analyses

There will be no formal interim analysis; however, all preliminary safety, tolerability, and available PK/PD data will be reviewed internally prior to each dose escalation and prior to transitioning to MAD dosing. Dose escalation can only occur after the Safety and Dose Escalation Committee (SDEC) has found that the safety, PK/PD profiles are supportive to proceed with the evaluation of the next higher dose level. The details of internal review process to support dose-escalation are included in the SDEC charter document.

After each cohort, the data will be reviewed – the data consists of the PK, RO, relationship between PK and RO, and safety data. At each cohort dose review, a dose will be proposed that meets the RO requirements for the next dosing cohort. Non-compartmental analysis (NCA) PK analysis will be performed to obtain PK parameters.

Beginning with the second dose in Part 1 and each subsequent dose throughout the study, the Bayesian probability of any individual participant exceeding the C_{max} No Observed Adverse Effect Level (NOAEL) exposure of 93.9 µg/mL (Protocol Section 5.5.1) at that dose will be calculated, using the accumulated PK data of participants receiving GSK3732394 among the previous cohorts. Observations on placebo will be excluded. This probability, together with safety and tolerability data of the preceding cohorts, will be used to help selection of the next dose. The Bayesian probability of exceeding the C_{max} threshold can be calculated for additional potential doses to aid in dose selection if necessary.

The Bayesian probability will be based on Whitehead's model shown below [Whitehead, 2001] using non-informative priors for the model parameters.

$$y_i = \theta_1 + \theta_2 d_i + \varepsilon_i$$

Where y_i is log-PK of i-th participant, d_i is the log-dose administered to i-th participant. θ_1 and θ_2 are population intercept and slope, respectively. ε_i is the random error of the i-th participant.

For the prediction of the second dose in Part 1 and Part 2, θ_2 will be assumed to equal 1 (representing a dose proportionality assumption). This will allow for the estimation of the remaining parameters of the model using data from only one dose level.

3.2. Final Analyses

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

1. All participants at the time of termination of the study have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility	• Study Population
Enrolled	All participants who passed screening and were randomized. Note: Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Safety	All participants who received at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received. Note: Participants who were not randomized but received at least one dose of study treatment should be listed.	• Study Population • Safety
Pharmacokinetic (PK)	All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK • PD

Refer to **Section 11.10**: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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 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 listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF (ClinBase).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptors			
RandAll NG		Data Displays for Reporting	
Code	**Description**	**Description**	**Order in TLF**
Part 1			
A	GSK3732394 Single dose level 1	GSK3732394 Single Dose 10 mg	1
B	GSK3732394 Single dose level 2	GSK3732394 Single Dose 20 mg	2
C	GSK3732394 Single dose level 3	GSK3732394 Single Dose 80 mg	3
P	Placebo	Single Dose Placebo	4

NOTES:

- Order represents treatments being presented in TLF, as appropriate.

5.2. Baseline Definitions

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. The Table below illustrates this rule for the planned Study Assessments. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Parameter	**Study Assessments Considered as Baseline**			**Baseline to use in Data Display**
	Screening	**Day -1**	**Day 1 (Pre-Dose)**	
Part 1				
Vital Signs, ECG	X		X	Day 1 (Pre-Dose)
PK sample, PD Sample			X	Day 1 (Pre-Dose)
Lab Assessments	X	X		Day -1

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Reporting Standards for Missing Data
11.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, concomitant medications, and exposure will be based on GSK Core Data Standards. Details of the planned displays are presented in Section 11.10: List of Data Displays.

7. SAFETY ANALYSES

The safety analyses will be based on the safety population, unless otherwise specified. All details of the planned displays are provided in Section 11.10: List of Data Displays. Unless otherwise specified, endpoints/variables will be summarized using descriptive statistics and listed.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Section 11.10: List of Data Displays.

AEs will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA) V22.1. AEs will be graded by the investigator according to the Division of AIDS (DAIDS) Criteria Version 2.1.

Injection site reactions will be reported as adverse events and included in the adverse events displays. Multiple symptoms of injection site reactions will be reported as separate adverse events for each reported symptom.

A summary of non-serious AEs that occurred in strictly 5% of the participants or above will be provided (even with the limited sample size of the study, no rounding for the percentage will be used in terms of 5% threshold).

A summary of number and percentage of participants with any adverse event by maximum grade will be produced. AEs will be sorted by PT in descending order of total incidence. The summary will use the following algorithms for counting the participant:

- Preferred term row: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- Any event row: Each participant with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

The following listings will be provided:

- All adverse events
- Subject Numbers for Individual AEs

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests (with lymphocyte subset [CD4/CD8/CD3]), Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Section 11.10: List of Data Displays. Haematology, clinical chemistry and urinalysis parameters collected are listed below:

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Lymphocyte Phenotype Absolute number and Percent of: CD3+ CD4+ CD8+
Clinical Chemistry	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Amylase
	Lipase			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed)[2] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] • Creatinine clearance (CrCL) for GFR estimation • The results of each test must be entered into the CRF.			

Laboratory toxicity grading will follow DAIDS grading criteria. Parexel data management will apply the grading in the SDTM dataset.

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Section 11.10: List of Data Displays.

7.3.1. Vital Signs

Vital sign values and change from baseline will be summarized. In addition, the number of subjects with worst case vital sign results relative to potential clinical importance (PCI) criteria post-baseline relative to baseline will be summarized by test and category.

7.3.2. Electrocardiograms

A summary of the number and percentage of subjects of all ECG findings will be displayed by treatment. Additionally, summary statistics of ECG values and change from baseline in ECG values will be presented.

7.3.3. Liver Events

The number of events does not support a summary. Liver monitoring/stopping event reporting will therefore only be listed for participants with liver events. In addition, listings will be produced for medical conditions and substance use for participants with liver events.

8. PHARMACOKINETIC ANALYSES

All PK analyses planned for the study are either part of the secondary or exploratory objectives. Due to study termination, only secondary PK analyses will be reported. The PK analyses will be based on the PK population, unless otherwise specified.

8.1. Pharmacokinetic Parameter Definitions and Summaries

8.1.1. Endpoint / Variables

8.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 11.5.3 Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin version 8.0. All calculations of non-compartmental parameters for the final analysis will be based on planned sampling times. Planned sampling times will be used due to early termination of the study and the frequency of PK sampling times in Part 1. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
C_{max}	Maximum observed concentration, determined directly from the concentration-time data.
t_{max}	Time to reach C_{max}, determined directly from the concentration-time data.
t_{lag}	Lag time before observation of drug concentrations (after single dose only)
C_{last}	last observable concentration
t_{last}	time of last quantifiable concentration
$t_{1/2}$	Apparent terminal phase half-life calculated as $t_{1/2} = \frac{\ln 2}{\lambda_z}$ (NOTE: λ_z is the terminal phase rate constant).
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the loge trapezoidal rule for each decremental trapezoid.
$AUC_{(0-\infty)}$	Area under the concentration-time curve extrapolated to infinity will be calculated (after single dose only) as: $AUC_{(0-\infty)} = AUC_{(0-t)}+C(t)/\lambda_z$ (NOTE: λ_z is the terminal phase rate constant).
$\%AUC_{ex}$	[The percentage of $AUC_{(0-\infty)}$ obtained by extrapolation ($\%AUC_{ex}$) will be calculated as: $[AUC_{(0-\infty)} - AUC_{(0-t)}] / AUC_{(0-\infty)} \times 100$
CL/F	Apparent Clearance

NOTES:

- Additional parameters may be included as required.

8.1.2. Summary Measure

- All the derived PK parameters will be summarized through descriptive statistics.
- Part 1 (single dose): $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $\%AUC_{ex}$, t_{max}, t_{lag}, $t_{1/2}$, C_{max}, C_{last}, t_{last}, CL/F

8.1.3. Population of Interest

These descriptive summaries will be based on the PK population.

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

Only completely administered doses of treatment will be considered for analysis. Participants may be replaced until the desired cohort size is attained. No imputation will be done for missing data after a participant withdrawal.

8.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Section 11.10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.2. Statistical Analysis of derived PK Parameters

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

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, (CPMS) and Statistical analyses of the pharmacokinetic parameters will be the responsibility of the Biostatistics Department.

8.2.1. Endpoint / Variables

$AUC_{(0-\infty)}$ and C_{max} in the single dose study part.

8.2.2. Summary Measure

The summary measure will be the point estimates and 90% CIs of mean slopes of log_e(dose) in the single dose study part.

8.2.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the PK population, unless otherwise specified.

8.2.4. Strategy for Intercurrent (Post-Randomization) Events

Only completely administered doses of treatment will be considered for analysis. Analyses will be based on available PK parameters. No imputation will be done for missing PK parameters for any participant.

8.2.5. Statistical Analyses / Methods

8.2.5.1. Statistical Methodology Specification

- The following statistical analyses will only be performed if sufficient data is available (i.e. if subjects have well defined plasma profiles).
- Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation Department, (CPMS) and Statistical analyses of the pharmacokinetic parameters will be the responsibility of the Biostatistics Department.

Pharmacokinetic Statistical Analyses - Dose Proportionality in single dose (Power Model)
Endpoint / Variables
• For SAD part: $AUC_{(0-\infty)}$, C_{max}
Model Specification
• Power model $y = \alpha * dose^{\beta}$ where y denotes the PK parameter being analyzed and dose denotes the total dose administered to a subject. • log_e transformed data will be analyzed by fitting the following linear model: $log_e y = log_e \alpha + \beta\ log_e dose$ • Data from all available doses in each part of the study will be considered.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored.
Model Results Presentation
Estimates of slope β will be reported along with corresponding 90% confidence intervals. If the CI contains 1 then we shall assume Dose Proportionality to hold.

9. PHARMACODYNAMIC ANALYSES

9.1. Pharmacodynamic Parameters and Summaries

The primary Pharmacodynamic measure is CD4 receptor occupancy (%RO) after single dose administration. Secondary measures include the component parameters of the %RO calculation and measures of activated T-cells.

9.1.1. Endpoint / Variables

CD4 receptor occupancy (%RO), component parameters used to calculate %RO, and active T-cells. The parameters are measured via flow cytometry and are reported as median fluorescence intensity.

9.1.2. Summary Measure

The following PD parameters will be summarized descriptively by treatment at each timepoint and also as change from baseline.

Parameter	Note
CD3+CD8+CD25+ (%CD8+)	Measures activated T-cell
CD3+CD8+ CD4(ADX6940)_AF647 MFI	Used in %RO calculation
CD3+CD4(OKT4)+CD25+ (%CD4(OKT4))	Measures Activated T-cell
CD3+CD8- CD4(OKT4)_PE MFI	Used in %RO calculation
CD3+CD8- CD4(ADX6940)_AF647 MFI	Used in %RO calculation
CD3+CD8- CD4(ADX6940)_AF647 Adjusted MFI	Used in %RO calculation
% Free	Calculated % Free
%RO	Calculated % RO

NOTE:
Additional parameters may be included as required.

9.1.3. Population of Interest

The primary pharmacodynamics analyses will be based on the PK population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

Since %RO is being reported descriptively, missing values will not be imputed and summaries will be based on observed data.

9.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Section 11.10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

10. REFERENCES

- Whitehead J. et al., Easy-to-implement Bayesian methods for dose-escalation studies in healthy participants, Biostatistics, 2, 47cs, 2, 47v 2001

11. APPENDICES

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

N/A as per-protocol population is not defined as an analysis population.

11.2. Appendix 2: Schedule of Activities

The following is the protocol-defined Schedule of Activities pertaining the Part 1 of the study.

Table 2 SCREENING AND FOLLOW-UP/EARLY DISCONTINUATION ASSESSMENTS (Part 1 and Part 2)

Procedure	**Screening** (up to 30 days prior to Day 1) [1]	**Follow-up/Early Discon Visit** (~28 days post last dose)	***Notes*** *Follow-up Visit to occur approximately 28 days after last study drug* administration or 5 half-lives (as determined from Part 1 PK data), whichever is longer.
Outpatient Visit	X	X	
Informed Consent	X		
Inclusion and Exclusion Criteria	X		
Demography	X		
Medical History	X		
Full Physical Examination (Including Height and Weight at the screening visit)	X		*Additional examinations may be performed, or brief examinations made full examinations, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).*
Target/Brief Physical Examination		X	
12-lead ECG	X	X	• *Triplicate ECGs will be used to determine participant eligibility at screening.* • *Additional tests may be performed by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Vital signs	X	X	
Urine Drug Screen	X		
Alcohol Screen	X		
Cotinine Screen	X		
Pregnancy Test	X	X	
HIV, Hep B and Hep C Screen	X		
Tuberculosis Test	X		
Laboratory assessments	X	X	
Pharmacokinetic sample		X	
Pharmacodynamic sample		X	
Anti- GSK3732394 antibodies		X	
Adverse Event Review	X	X	*The collection of SAEs will be from the screening visit to the end of the study*

Procedure	Screening (up to 30 days prior to Day 1) [1]	Follow-up/Early Discon Visit (~28 days post last dose)	*Notes*
			Follow-up Visit to occur approximately 28 days after last study drug administration or 5 half-lives (as determined from Part 1 PK data), whichever is longer.
Concomitant Medication Review	X	X	

1. Screening must be performed within 30 days prior to receiving the dose of GSK3732394/PBO on Day 1

Table 3 Part 1 - All Cohorts Inpatient Days -1 to Day 14

Procedure	Day																						
	Day -1	Day 1								2	3	4	5	6	7	8	9	10	11	12	13	14
		Pre-dose	0 h	0.5 h	1 h	2 h	4 h	8 h	12h	24h	48h	72h	96h	120h	144h	168h	192h	216h	240h	264h	288h	312h
Admission to Unit	X																					
Discharge from Unit																						X
Urine Drug Alcohol/Screen/Cotinine	X																					
Brief Physical Exam	X									X						X						X
Vital signs		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X						X		X	X						X						X
Pregnancy Test	X																					
Meals	*Per site usual practice*																					
Laboratory assessments[1]	X									X	X		X			X			X			X
Randomization		X																				
Drug administration			X																			
Pharmacokinetic sample[2]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamic		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Day																					
		Day 1								2	3	4	5	6	7	8	9	10	11	12	13	14
	Day -1	Pre-dose	0 h	0.5 h	1 h	2 h	4 h	8 h	12h	24h	48h	72h	96h	120h	144h	168h	192h	216h	240h	264h	288h	312h
sample[2]																						
Antidrug Antibody sample	X														X			X				X
Biomarker sample[3]	X																					
Urine sample[4]	X		X																			
SAE/AE Review[5]	<==========																					==========>
Con Med Review	<==========																					==========>

1. Laboratory assessments include hematology (with lymphocyte subset [CD4/CD8/CD3], clinical chemistry and urinalysis.
2. The number of PK and PD sampling time points may be reduced/extended in subsequent dosing groups once human PK data are available from initial SAD dosing cohorts. An aliquot of the PK serum sample will be used for GSK3732394-related material (serum metabolites) identification.
3. Serum for biomarkers of immune activation will be collected at baseline and post-treatment in the event of clinical symptoms
4. Urine will be collected at Day -1 (10mL) and for 24 hours after dose administration for GSK3732394-related material identification in the highest dose cohort only. Details for urine collection and interval is included in the SRM.
5. To include assessment of injection site(s) as appropriate (see also Protocol Section 3.3.1 and Protocol Section 8.1, and the SRM).

Table 4 Part 1 - Outpatient Visit Days 17, 21, 24, 28

Procedure	Day			
	17	21	24	28[1, 2]
Brief Physical Exam	X	X	X	X
Vital signs	X	X	X	X
12-lead ECG	X			X
Pregnancy Test				X
Laboratory assessments[3]	X	X	X	X
Pharmacokinetic sample[4,5]	X	X	X	X
Pharmacodynamic sample[4,5]	X	X	X	X
Antidrug Antibody sample		X		X
Biomarker sample[6]				
Adverse Event Review[7]	<==========			==========>
Con Med Review	<==========			==========>

6. In the event of terminal half-life longer than predicted, PK/PD and laboratory assessments will occur every four days until an estimated 5 half-lives have elapsed
7. For participants with no ongoing AEs or Vital Sign/Laboratory measures of clinical concern at Day 28 Visit, these procedures and those listed in Table 2 Screening and Follow-up/Early Discontinuation" for Follow-up/Early Discontinuation Visit (~28 days post last dose) may be considered the same.
8. Laboratory assessments include hematology (with lymphocyte subset [CD4/CD8/CD3], clinical chemistry and urinalysis.
9. An aliquot of this PK serum sample will be used for GSK3732394-related material (serum metabolites) identification.
10. PK samples collection on Days 17, 21 and 24 are conditional on the PK assessment at up to Day 7 during the conduct of the study and may be adjusted as data become available.
11. Serum for biomarkers of immune activation will be collected at baseline and post-treatment in the event of clinical symptoms
12. To include assessment of injection site(s) as appropriate (see also Protocol Section 3.3.1 and Protocol Section 8.1, and the SRM).

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Table 5 Part 2 - All Cohorts Inpatient Days -1 to Day 17

Procedure	Day																												
	Day -1	Day 1								2	3	4	5	6	7	8		9	10	11	12	13	14	15		16	17
		Pre-dose	0 h	0.5 h	1 h	2 h	4 h	8 h	12h	24h	48h	72h	96h	120h	144h	Pre-dose	0 h	24h	48h	72h	96h	120h	144h	Pre-dose	0 h	24h	48h
Admission to Unit	X																										
Urine Drug/ Cotinine/Alcohol Screen	X																										
Brief Physical Exam	X									X					X								X				
Vital signs		X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
12-lead ECG	X						X		X	X	X					X								X			
Pregnancy Test	X																										
Meals	*Per site usual practice*																										
Laboratory assessments[1]	X									X	X		X			X		X		X				X		X	
Randomization		X																									
Drug administration			X														X								X		
Pharmacokinetic sample[2]		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
Pharmacodynamic sample		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
Antidrug Antibody sample	X															X								X			
Biomarker sample[3]	X																										
Urine sample[4]	X																										
Adverse Event Review[5]	<==========																										==========>
Con Med Review	<==========																										==========>

1. Laboratory assessments include hematology (with lymphocyte subset [CD4/CD8/CD3], clinical chemistry and urinalysis.
2. An aliquot of the PK serum sample will be used for GSK3732394-related material (serum metabolites) identification. Refer to the windows allowance agreement attached to the SRM for timing of trough samples to be drawn on non-dosing days.
3. Serum for biomarkers of immune activation will be collected at baseline and post-treatment in the event of clinical symptoms
4. Urine will be collected at Day -1 (10mL) and for 24 hours after dose administration for GSK3732394-related material identification after the 4th MAD dose. Details for urine collection and interval is included in the SRM.
5. To include assessment of injection site(s) as appropriate (see also Protocol Section 3.3.1 and Protocol Section 8.1, and the SRM).

11.3. Appendix 3: Assessment Windows

- Nominal time will be used for all analysis except PK analysis where planned and actual time will be used.

11.3.1. Definitions of Assessment Windows for Analyses

The visit assigned to the assessment as entered in the eCRF (nominal visit) will be used for reporting.

11.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

11.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment.

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
In-Patient	Study Treatment Start Date < Date ≤ Study Treatment Stop Date +14 Days
Out-Patient Follow up	Date > Study Treatment Stop Date + 14 Days

11.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

11.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date plus 14 days (in-patient setting) • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 14 days. • Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date + 14 days.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	US1SALX00259
HARP Compound	Compound: GSK3732394, study: 207863, reporting effort: final_01
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1).	
Generation of RTF Files	
• RTF files will be generated for SAC.	

11.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats

• 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, unless otherwise stated.
• 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.
  • Display all numeric variables with the same number of decimal places as the collected precision.
  • Display minimum and maximum values with the same number of decimal places as the collected precision.
  • Display the mean and percentiles (e.g. median, Q1, and Q3) with one additional decimal place.
  • Display the standard deviation and standard error with two additional decimal places.
  • Within a column, align all data values or summary statistics along the decimal point.
  • The reported precision for PK concentration data will be 1 decimal place but may be altered by parameter depending on the significant digits.

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.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and figures. • All unscheduled visits will be included in listings.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

11.5.3. Reporting Standards for Pharmacokinetic Data

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to [SOP_514512]. Note : Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	None. All PK parameters will be derived by the CPMS Pharmacokineticist.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to [Standards for Handling NQ Impacted PK Parameters].
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Loge-transformed data: N, n, geometric mean, 90% CI of geometric mean, standard deviation (SD) of loge transformed data and between subject geometric coefficient of variation (CVb (%)) will be reported. CVb (%) = $\sqrt{}$ (exp(SD2) – 1) * 100 [NOTE: SD = SD of loge transformed data] Parameters Not Being Loge Transformed: Tmax and T1/2.

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Analysis Time Point
• 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 values within a time window (as per Section 11.3.1) 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. • Participants having both High and Low values for Normal Ranges at any post-baseline visit 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 First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

11.6.2. Study Population

Treatment Compliance
• Treatment compliance will be evaluated by comparing randomized and actual doses of each participant in the listing.
Extent of Exposure
• For the single dose portion of the study each participant receives a single dose. Therefore, no cumulative dose will be calculated per participant.

11.6.3. Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcF is machine read, 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 (ClinBase), corrected QT intervals by Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcF will be derived as : $$QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

11.6.4. Pharmacokinetic

PK parameters
• The PK Population will include all subjects who undergo PK sampling and have evaluable PK assay results. • See Section 8.1 for derived Pharmacokinetic parameters

11.6.5. Pharmacodynamic

% Receptor Occupancy
CD4 Free Receptor (%Free) and CD4 Receptor Occupancy (%RO) will be calculated as follows: $$\%Free = \left(\frac{\frac{\Delta CD3^{+}CD8^{-}\ ADX6940\_AF647\ MFI\ post\ dose}{\Delta CD3^{+}CD8^{-}\ ADX6940\_AF647\ MFI\ pre\ dose}}{\frac{CD3^{+}CD8^{-}\ OKT4\_PE\ MFI\ post\ dose}{CD3^{+}CD8^{-}\ OKT4\_PE\ MFI\ pre\ dose}} \right) * 100$$ $$\%RO = \left(1 - \frac{\frac{\Delta CD3^{+}CD8^{-}\ ADX6940\_AF647\ MFI\ post\ dose}{\Delta CD3^{+}CD8^{-}\ ADX6940\_AF647\ MFI\ pre\ dose}}{\frac{CD3^{+}CD8^{-}\ OKT4\_PE\ MFI\ post\ dose}{CD3^{+}CD8^{-}\ OKT4\_PE\ MFI\ pre\ dose}} \right) * 100$$ Note: The adjusted MFI (Δ) will be used to calculate Free Receptor and Receptor Occupancy values in the AF647 channel. Delta MFI values will be calculated as follows: (CD3+CD8- CD4(ADX6940)_AF647 MFI) - (CD3+CD8+ CD4(ADX6940)_AF647 MFI). %Free and %RO will be in the SDTM data.

% Receptor Occupancy
Limit of Detection (LOD) of the Receptor Occupancy Assay
The limit of detection (LOD) of the receptor occupancy assay will be calculated using the cumulative placebo data of the study. The limit of detection (LOD) will be calculated as follows. For each placebo subject the average of (3+8- 647 Delta / 3+8- OKT4_PE) will be calculated across all timepoints where both measures are available. This average value will be used to calculate %RO at each timepoint *i* as: $\%RO_i=(1-(3+8\text{- }647\ Delta_i/\ 3+8\text{- }OKT4\_PE_i)/Mean(3+8\text{- }647\ Delta_i/\ 3+8\text{- }OKT4\_PE_i))*100.$ The subject standard deviation ($SD_{subject}$) of these $\%RO_i$ values will be calculated for each placebo subject and $LOD_{subject}$ will be calculated as: $LOD_{subject}=Mean(\%RO_i)$[1] + $3*SD_{subject}$ The cumulative LOD will be calculated by averaging the $LOD_{subject}$ across all placebo subjects. Imputed %RO is defined as 0 for all timepoints where the Assay-Reported %RO is below LOD except for the timepoint immediately prior to an Assay-Reported %RO above LOD and the timepoint immediately after an Assay-Reported %RO above LOD. The imputed %RO for these timepoints will be ½ of the LOD. Assay-reported %RO will be used for summaries and both assay-reported and imputed %RO will be listed.

[1] Note: $Mean(\%RO_i)=0$ by definition using the above average adjustment

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined having completed all phases of the study including the last visit and the last scheduled procedure shown in the Schedule of Activities. • Withdrawn subjects may be replaced in the study. • All available data from participants 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. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

11.7.2. 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 participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. Handling of Missing and Partial 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: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events.
	  ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• 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.

Concomitant	• Partial dates for any concomitant medications recorded in the CRF will be imputed

Element	Reporting Detail
Medications/ Medical History	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.

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values

Element	Reporting Detail
Laboratory Values and Adverse Events	• The Division of AIDS (DAIDS) grading for severity of laboratory toxicities and clinical adverse events, version 2.1, July 2017 will be used to assign grades to laboratory values. • When deriving the Grading for severity of laboratory toxicity only numeric criteria are considered. The following note will be included in the listing including laboratory severity output: "Grades were derived based on numeric criteria as defined in DAIDS Version 2.1 and did not take into consideration of clinical signs or symptoms which is needed for the final grade associated with the adverse event." • Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

11.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		450
Absolute PR Interval	msec	110	220
Absolute QRS Interval	msec	75	110
QTc Interval (Bazett)	msec		450
QTc Interval (Fridericia)	msec		450
Change from Baseline			
Increase from Baseline QTc	msec		60

11.8.3. 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

11.9. Appendix 9: Abbreviations & Trade Marks

11.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
LOD	Limit of Detection
MMRM	Mixed Model Repeated Measures
MFI	Median Fluorescence Intensity
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan

Abbreviation	Description
RAMOS	Randomization & Medication Ordering System
RO	Receptor Occupancy
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
Tmax	Time Taken to Maximum Observed Plasma Drug Concentration
Tlag	Lag time before observation of drug concentrations
t1/2	Terminal phase half-life
tau	Dosing interval
Cmax	Maximum observed concentration
Ctau	Trough concentration
Clast	last observable concentration
tlast	time of last quantifiable concentration
AUC	Area under the concentration-time curve
CL/F	Apparent Clearance
NOAEL	No Observed Adverse Effect Level
DAIDS	Division of AIDS

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.3	NA
Safety	3.1 to 3.17	NA
Pharmacokinetic	4.1 to 4.3	4.1 to 4.3
Pharmacodynamic	6.1 to 6.2	NA
Section	**Listings**	
ICH Listings	1 to 25	
Other Listings	26 to 29	

11.10.2. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

11.10.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	Safety	ES4	Summary of Subject Disposition at Each Study Epoch	ICH E3	SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
Protocol Deviation					
1.4.	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.5.	Screened	SP1	Summary of Study Populations	IDSL	SAC
Demographic and Baseline Characteristics					
1.6.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.7.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC

11.10.4. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	Safety	AE5B	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term	ICH E3	SAC
3.2.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT ‘	SAC
Laboratory: Chemistry					
3.3.	Safety	LB1	Summary of Clinical Chemistry Data		SAC
3.4.	Safety	LB1	Summary of Clinical Chemistry Changes from Baseline		SAC
3.5.	Safety	LB16	Summary of Worst Case Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Hematology					
3.6.	Safety	LB1	Summary of Hematology Data		SAC
3.7.	Safety	LB1	Summary of Hematology Changes from Baseline	ICH E3	SAC
3.8.	Safety	LB16	Summary of Worst Case Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Urinalysis					
3.9.	Safety	UR1	Summary of Urine Data		SAC
3.10.	Safety	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ECG					
3.11.	Safety	EG2	Summary of ECG Values		SAC
3.12.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
3.13.	Safety	EG11	Summary of Increase in QTc Values Post-Baseline Relative to Baseline by visit and Category	Add Visit Column before category. Replace "Maximum" in shell program with summary per visit. Use the following categories: • <=10ms • >10ms-20ms • >20-30ms • >30-60ms • >60ms	SAC
3.14.	Safety	EG1	Summary of ECG Findings	IDSL	SAC
Vital Signs					
3.15.	Safety	VS1	Summary of Vital Signs		SAC
3.16.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC
3.17.	Safety	VS7	Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline	IDSL	SAC

11.10.5. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK	PK01	Summary of GSK3732394 Plasma PK Concentration-Time Data by Treatment		SAC
PK Parameters					
4.2.	PK	PK06	Summary of Derived GSK3732394 Plasma Pharmacokinetic Parameters (non-transformed and log-transformed) by Treatment		SAC
PK Statistical Analysis Table					
4.3.	PK	mid207187 Table 4.4	Summary Results of Single Dose Proportionality Assessment Using Power Model	(reference study mid207187 Table 4.4)	SAC

11.10.6. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.1.	PK	PK16a	Individual GSK3732394 Plasma Concentration-Time Plots (Linear and Semi-Log) by Treatment	Overlay all individual profiles per treatment in a plot. Separate plots by treatment.	SAC
4.2.	PK	PK17	Median GSK3732394 Plasma Concentration-Time Plots (Linear and Semi-Log)		SAC
4.3.	PK	PK18	Mean GSK3732394 Plasma Concentration-Time Plots (Linear and Semi-Log)		SAC

11.10.7. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PD					
6.1.	PK	LB1	Summary of Pharmacodynamic Parameters by Treatment		SAC
6.2.	PK	LB1	Summary of Pharmacodynamic Parameters Changes from Baseline by Treatment		SAC

11.10.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	Screened	ES9	Listing of Subjects Who Were Rescreened		SAC
3.	Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
4.	Safety	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC
5.	Safety	TA1	Listing of Randomized and Actual Treatment	IDSL	SAC
Protocol Deviations					
6.	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
7.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Demographic and Baseline Characteristics					
8.	Safety	DM2	Listing of Demographic Characteristics	ICH E3	SAC
9.	Safety	DM9	Listing of Race	ICH E3	SAC
Concomitant Medications					
10.	Safety	CM3	Listing of Concomitant Medications	IDSL	SAC
Exposure					
11.	Safety	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12.	Safety	AE8	Listing of All Adverse Events	ICH E3	SAC
13.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
Serious and Other Significant Adverse Events					
14.	Safety	AE8CPA	Listing of Serious Adverse Events (Fatal & Non-Fatal)	ICH E3	SAC
15.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study	ICH E3	SAC
Hepatobiliary (Liver)					
16.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	IDSL	SAC
17.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline	IDSL	SAC
18.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC
19.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL list available substance use data for subjects with liver events	SAC
All Laboratory					
20.	Safety	LB5A	Listing of All Laboratory Data	ICH E3	SAC
ECG					
21.	Safety	EG3	Listing of All ECG Values		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
22.	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
23.	Safety	EG5	Listing of All ECG Findings		SAC
Vital Signs					
24.	Safety	VS4	Listing of All Vital Signs		SAC
25.	Safety	VS4	Listing of All Vital Signs for Subjects with Values of Potential Clinical Importance		SAC

11.10.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
26.	PK	PK07	Listing of GSK3732394 Plasma PK Concentration-Time Data		SAC
27.	PK	PK13	Listing of Derived GSK3732394 Plasma PK Parameters		SAC
PD					
28.	PK	PK07	Listing of Assay-Reported and Imputed %Receptor Occupancy	Replace Concentration in Example Shell with %RO and add Column for Imputed %RO	SAC
Immunogenicity					
29.	PK	IMM2	Listing of Immunogenicity Results		SAC